The New England
Journal of Medicine

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Volume 237 OCTOBER 9, 1947 Number 15

STREPTOMYCIN THERAPY IN 52 CASES OF BACTERIAL INFECTION*

LEWIS W. KANE, M.D.,† AND GEORGE E. FOLEY‡

BOSTON

STREPTOMYCIN, an antibiotic agent obtained from certain strains of *Actinomyces griseus*, was first described by Schatz, Bugie and Waksman[1] in 1944. Immediate interest was attracted to this agent because of its effectiveness in vitro against bacteria that had previously been resistant to the action of known antibiotic and chemotherapeutic agents. Animal studies have demonstrated that the toxicity of streptomycin is of a relatively low order,[2] and the results in the treatment of experimental infections have proved its effectiveness in vivo.[2–5] Clinical trials in the past two years have confirmed its low toxicity and demonstrated its value in the treatment of infections known to be resistant to the action of penicillin and the sulfonamides, such as those produced by gram-negative bacilli. Among the human infections known to respond to streptomycin treatment are tularemia,[6, 7] meningitis due to *Haemophilus influenzae*[8, 9] and urinary-tract infections due to gram-negative bacilli.[8, 10] The results of treatment of 1000 miscellaneous cases have recently been reviewed by the Committee on Chemotherapeutics of the National Research Council.[11]

It is the purpose of this paper to report in detail the results obtained in 52 cases treated with streptomycin.§ In this group are included urinary-tract infections, meningitis and epiglottitis due to *H. influenzae*, bronchiectasis, nonspecific urethritis and 1 case of septicemia caused by *Pseudomonas aeruginosa*.

MATERIAL AND METHODS

All patients treated with streptomycin were hospitalized at the Massachusetts General Hospital or the Massachusetts Eye and Ear Infirmary.¶ They were selected on the basis of the infecting organism after careful bacteriologic study. Most patients had previously been treated with penicillin or one of the sulfonamides and had failed to make a satisfactory clinical response. In most cases streptomycin was administered intramuscularly. Topical and aerosol streptomycin were used in certain cases in which they were considered to be of possible value.

Determinations of streptomycin sensitivity and body-fluid levels of the drug were carried out, when indicated, according to the method described by Price, Nielsen and Welch.[12]

URINARY-TRACT INFECTIONS

Pyelonephritis and Cystitis

Thirty-eight cases of pyelonephritis and 2 cases of cystitis were treated with streptomycin (Table 1). These cases were selected on the basis of infections due to gram-negative bacilli. In 32 cases the infecting organism belonged to the colon-aerogenes group. Of the remainder, 2 were due to *Ps. aeruginosa* and 2 to *Proteus vulgaris*, and 4 were mixed infections due to *Escherichia coli* in combination with *Ps. aeruginosa* in 2 cases and *Pr. vulgaris* in 2. No cases were treated in which inlying catheters were being used. Cases with nonobstructing renal calculi or partial ureteral strictures were not excluded in this study, since it seemed important to determine the effect of streptomycin in the presence of these complications. Except when contraindicated, sulfonamides and less frequently mandelic acid and penicillin were employed in all cases prior to the initiation of streptomycin therapy.

A 0.1 per cent streptomycin solution in physiologic saline was given intramuscularly on a four-hour schedule, but the 2-a.m. dose was usually omitted because it was observed that effective urinary levels were maintained during the 10-p.m. to 6-a.m. interval. The total dosage varied from a minimum of 0.5 to a maximum of 2.0 gm. a day. At first all cases were treated with 1 gm. daily for ten days, but as more experience was gained, it was found that smaller doses (0.5 gm.)

*From the Department of Medicine and the Department of Pathology and Bacteriology, Massachusetts General Hospital, and the Department of Bacteriology and Immunology, Harvard Medical School.

†Assistant in bacteriology and immunology, Harvard Medical School; assistant in medicine, Massachusetts General Hospital.

‡Assistant bacteriologist, Massachusetts General Hospital.

§The streptomycin used in these studies was provided by the National Research Council from supplies assigned for clinical investigations recommended by the Committee on Therapeutics and Other Agents.

¶This study was made possible by the close co-operation of the visiting and house staffs of the medical, surgical and pediatric services of the Massachusetts General Hospital and Massachusetts Eye and Ear Infirmary. We are indebted to Mrs. W. C. Burrage for aid in the technical work and the preparation of the manuscript.

given for as little as three or four days were sufficient in cases in which the infecting organisms were extremely sensitive. In cases in which it was impossible to obtain the sensitivity of the infecting organism prior to the institution of therapy, 1 gm. daily was used as an initial dose, and the response three days and in 1 each within four and five days.

The duration of therapy varied according to the rapidity with which the organisms disappeared from the urine. It soon became apparent that it was not necessary in most cases to continue treatment for more than three days after the urine first became

TABLE 1. *Results of Streptomycin Therapy in 40 Cases of Pyelonephritis and Cystitis.*

Case No.	Age	Duration of Disease	Renal Complications	Etiologic Agent	Inhibiting Level of Streptomycin	Previous Therapy	Streptomycin Dosage	
							daily	total
	yr.	yr.			*micrograms/100 cc.*		gm.	gm.
1	42	1/12	—	*Esch. coli*		Penicillin	1.0	12.6
2	26	22	Renal calculi, hydronephrosis and hydroureter	*Esch. coli* *Pr. vulgaris*	2500 1500	Penicillin and sulfonamide	1.0–2.0	19.9
3	36	1/12	—	*Esch. coli* *Ps. aeruginosa*		Penicillin and sulfonamide	1.0	7.4
4	50	6/52	—	*Esch. coli*		Penicillin and sulfonamide	1.0	7.6
5	33	16	Renal calculi	*Esch. coli*		Sulfonamide	1.0	7.4
6	59	25/12	Hydroureters and stricture	*Esch. coli*		Penicillin and sulfonamide	1.0	4.3
7	38	2/12	—	*Esch. coli*		Sulfonamide	1.0	4.2
8	49	2/52	—	*Esch. coli*		Penicillin and sulfonamide	0.9	5.7
9	5.5	1	Bilateral hydronephrosis and hydroureters	*Esch. coli*	125	Penicillin and sulfonamide	0.5–1.0	5.7
10	38	6/365	—	*Esch. coli*		None	0.9	3.9
11	59	11	—	*Esch. coli*		Sulfonamide	1.0	5.4
12	38	6–7	—	*Esch. coli*		Penicillin and sulfonamide	1.0	5.6
13	35	8/12	Renal calculi	*Esch. coli*		Sulfonamide	1.2	10.0
14	58	14	Renal calculus	*Esch. coli*		None	0.5	2.3
15	40	16	Hydronephrosis and hydroureters	*Esch. coli*	2000	Sulfonamide	1.0	5.0
16	38	12	Hydroureters and dilated calyxes	*Esch. coli*	156	Sulfonamide	2.0	15.2
18	67	1/12	Renal calculi	*Pr. vulgaris*		Sulfonamide	1.0	6.8
19	43	7	Bilateral renal calculi	*Esch. coli* *Ps. aeruginosa*	2000	Sulfonamide	1.0	7.6
20	58	1	—	*Esch. coli*		Sulfonamide	1.0	8.0
21	62	12	—	*Esch. coli*		Sulfonamide	1.0	6.6
22	32	5	Partial ureteral stricture	*Esch. coli*	7.8	Penicillin and sulfonamide	1.0–2.0	10.0
23	22	2	Hypoplastic kidney	*Ps. aeruginosa*	31.2	Penicillin	1.2–2.0	9.2
24	69	11/365	Incontinence	*Esch. coli*		Sulfonamide	1.0	7.0
25	42	1/12	—	*Esch. coli*	15.6	Sulfonamide	0.5	4.0
26	56	1/12	—	*Esch. coli*	15.6	Penicillin and sulfonamide	1.0	4.4
27	69	4	Partial stricture of ureter	*Esch. coli*		Penicillin and sulfonamide	1.0	6.4
28	2	15/365	—	*Ps. aeruginosa*	125	Penicillin and sulfonamide	1.0	6.6
29	45	14/365	Cord bladder	*Esch. coli*	62.5	Penicillin and sulfonamide	1.0–1.2	7.0
30	36	8/365	—	*Esch. coli*	2000	Penicillin and sulfonamide	1.0	8.8
31	47	?	—	*Esch. coli*		None	1.0	7.0
32	55	17	Slight hydronephrosis	*Esch. coli*	15.6	Sulfonamide	0.5–1.0	7.0
33	36	1	—	*Esch. coli*		Sulfonamide	0.5	3.8
34	24	4	Dilated calyxes	*Esch. coli*		Sulfonamide	1.0	6.8
35	6	4	Dilated calyxes and pelves	*Esch. coli*	15.6	Penicillin and sulfonamide	1.0	7.6
36	40	15/365	—	*Esch. coli*	1.5	Penicillin and sulfonamide	1.0	10.8
37	67	3/12	—	*Esch. coli*		None	0.5–1.0	3.5
38	35	7	—	*Pr. vulgaris*		Penicillin and sulfonamide	1.0	8.0
39	50	16/12	Atonic bladder	*Esch. coli*		Sulfonamide	0.5	3.5
40	73	2	—	*Esch. coli* *Pr. vulgaris*		Sulfonamide	1.0	7.8
41	8	6/365	—	*Esch. coli*	15.6	Sulfonamide	1.0–1.8	15.1

assayed by daily urine cultures. When this method was used, the dosage was raised if there was no response within three or four days. The reliability of this method is indicated by the fact that of the 30 cured patients followed by daily cultures while on streptomycin therapy, the urine in 17 (57 per cent) became sterile within one day, in 8 (26 per cent) within two days,* in 3 (10 per cent) within sterile. In no case was therapy continued for more than eleven days.

Whenever possible, the fluid intake was restricted to 2000 to 3000 cc. daily. On the basis of the work done by Abraham and Duthie,[13] in which it was demonstrated that streptomycin is most effective in an alkaline medium, the urine was alkalinized in the majority of cases by means of sodium citrate. One teaspoonful of a 50 per cent solution was given orally three times daily. The reaction of each speci-

*In 4 of these cases the urine was not cultured until the second day, and hence may actually have been sterile on the day following the institution of streptomycin therapy.

men was checked by nitrazine paper. In most cases this dosage was sufficient to maintain an alkaline urine, but occasionally the daily dosage had to be increased to five teaspoonfuls. In the occasional case with pulmonary or peripheral edema, potassium salts were substituted for sodium citrate.

collate when blood agar or Endo's medium failed to show growth.

All cases were classified as cured, improved or unimproved. Cases in which the original infecting organism disappeared under therapy and for a minimum of one week after all therapy had been dis-

TABLE 1 (*Continued*).

CASE No.	RESULT	FIRST STERILE URINE CULTURE	FOLLOW-UP CULTURES		REACTIONS	REMARKS
			NO.	PERIOD		
		days		*days*		
1	Cure	2	5	26	Fever	
2	No improvement		10	11	Headache and vertigo	Resistant organisms
3	Cure	1	3	5	None	
4	Cure	1	10	106	None	
5	Cure	4	6	121	None	
6	Cure	1	5	122	None	
7	Cure	1	6	94	None	
8	Cure	1	5	58	None	
9	No improvement		1	1	None	
10	Cure	1	8	44	None	Sulfonamides contraindicated; *Str. faecalis* appeared after cessation of therapy; *Staph. albus* appeared after cessation of therapy.
11	Cure	1	0	57	None	
12	Cure	3	3	75	None	Gamma streptococci appeared on 75th day
13	Cure	1	11	100	None	
14	Cure	1	3	5	None	
15	No improvement		4	26	None	Resistant organism
16	Cure	2	4	66	Skin eruption	
18	Cure	1	5	44	None	
19	No improvement		1	63	None	Resistant organism
20	Cure	1	6	47	None	
21	Cure	1	10	16	None	
22	Cure	2	4	37	None	Patient became reinfected with *Ps. aeruginosa*
23	Cure	1	2	7	None	Patient pregnant during therapy
24	Improvement		4	6	None	Patient catheterized every 8 hr.; death from coronary disease.
25	Cure	3	3	20	None	
26	Cure	1	7	53	None	
27	Cure	1	3	37	None	
28	Cure	2	15	27	None	Inhibiting level increased to 500 microgm. during therapy
29	Improvement		7	16	None	Patient catheterized every 4 to 6 hr. and became infected with resistant *Ps. aeruginosa* (2000 microgm.) while on therapy
30	No improvement		1	1	None	Sulfonamides contraindicated; blood dyscrasia. Resistant organism
31	Cure	2	12	58	None	Chronic pyelonephritis; relapse after 56 days.
32	Cure	2	2	13	None	
33	Cure	2	3	10	None	
34	Improvement	3	1	41	None	
35	No improvement		22	59	None	Relapse on cessation of drug; no increase in resistance of organism.
36	Cure	5	5	8	Local pain	Death from pulmonary embolism
37	Cure		4	20	None	Gamma streptococci appeared 9 days after cessation of therapy
38	Cure	1	8	28	Local pain	
39	Cure	2	4	69	None	Cystitis
40	Cure	1	4	45	None	Cystitis
41	Improvement	2	2	23	None	Inhibiting level increased to 2000 microgm. during therapy

Clean voided urine specimens were obtained daily on male and catheterized specimens on female patients. At the beginning of this study all urine sediments were cultured in sodium thioglycollate in addition to the usual blood agar and Endo's medium. Sodium thioglycollate was chosen, since it has been shown experimentally that this substance, as well as glucose, reduces streptomycin activity.[14] This was soon discontinued, however, since in no case was a positive culture obtained in sodium thioglycollate when blood agar or Endo's medium failed to show growth.

All cases were classified as cured, improved or unimproved. Cases in which the original infecting organism disappeared under therapy and for a minimum of one week after all therapy had been discontinued were considered cured. It was believed that if the urine remained sterile for one week the infection would not relapse, since in the 30 cases considered cured on this basis, there was only one questionable relapse. This case, in which the urine again became positive for *Esch. coli* fifty-six days after therapy had been discontinued, may have represented reinfection rather than an actual relapse. The majority of cases were followed for periods longer than one week (Table 1). No case

was considered cured unless a minimum of two follow-up cultures were done. In most cases, more than two cultures and in some as many as fifteen were obtained over a period of several months. Cases were classified as improved when urine cultures did not become completely sterile, but in which there was a marked reduction in the colony count, as well as improvement in the urinary sediment. Cases were considered unimproved when there was neither clinical nor bacteriologic response to therapy.

The results of streptomycin therapy in 40 cases of urinary-tract infections when classified according to the criteria mentioned above were 75 per cent cured, 10 per cent improved and 15 per cent with no response. Thus, 85 per cent of all cases were definitely aided by streptomycin therapy. These figures indicate that good results may be expected in the majority of urinary-tract infections due to gram-negative bacilli, despite the fact that they have failed to respond to other antibiotic and chemotherapeutic agents. In this study the best results were obtained in cases with no structural damage to the urinary tract in which the infecting organism was sensitive to streptomycin. In this group of 21 cases 91 per cent were cured and 9 per cent improved (Table 2); there were no failures.

Moderate structural damage, such as dilated calyxes, slight hydronephrosis, partial stricture of a ureter or small nonobstructing renal calculi, did not seem to preclude a cure if the infecting organism was sensitive (Cases 5. 6, 13, 14, 16, 18, 22, 23, 27, 32 and 39).

Infections with organisms found to have resistance in vitro that was higher than the levels obtained in the urine were unimproved by streptomycin therapy (Cases 2, 15, 19 and 30). One patient (Case 41) in whom resistance was acquired during therapy had shown marked clinical and bacteriologic improvement prior to the development of resistance.

The duration of infection seemed to be of importance only in that it led to marked structural changes and the formation of obstructive renal calculi. One patient (Case 30) in whom the duration of the infection was only eight days, failed to respond, whereas another (Case 14) responded to streptomycin after having been infected for fourteen years.

In the improved group of 4 cases, the urine could not be completely sterilized in 2 (Cases 24 and 29), possibly because of the necessity of performing catheterizations every four to eight hours. An additional patient (Case 34) might have been cured had therapy been more intensive and prolonged. In only 1 patient (Case 41) could failure to sterilize the urine be attributed to the acquisition of streptomycin resistance by the infecting organism.

Of the 6 cases classified as unimproved, 3 (Cases 2, 15 and 19) were infected with streptomycin-resistant organisms, and in addition there were structural changes in the urinary tract, such as dilatation of the calyxes or ureters. Two of these patients (Cases 2 and 19), in addition to harboring resistant organisms and having structural damage, had renal calculi. Only 1 patient with no structural complications (Case 30) failed to respond. This patient was infected with an extremely resistant organism. Failures resulted in 2 patients (Cases 9 and 35) who had streptomycin-sensitive organisms and extensive renal damage as a result of long-standing infection.

Two cases were considered to have relapsed. One of these patients (Case 35) relapsed as soon as streptomycin was discontinued, undoubtedly because of extensive renal damage. In the other (Case 31), relapse after fifty-six days may actually have represented a reinfection.

It is of interest that 1 patient (Case 29) became reinfected with another organism while on streptomycin therapy, but this case required repeated catheterizations, and the reinfecting organism was a streptomycin-resistant *Ps. aeruginosa*. An additional patient (Case 22), with a partial stricture of the right ureter, was cured of an *Esch. coli* infection, but thirty-seven days later became reinfected with *Ps. aeruginosa*.

Case 41 deserves special comment. The patient was an eight-year-old child who came into the hospital in a comatose, moribund condition due to a fulminating *Esch. coli* pyelonephritis. The nonpro-

TABLE 2. *Results of Streptomycin Therapy in Cases with and Those without Urinary-Tract Damage.**

TYPE OF CASE	TYPE OF ORGANISM	NO. OF CASES	PATIENTS CURED		PATIENTS IMPROVED		PATIENTS UNIMPROVED		TOTAL PERCENTAGE CURED OR IMPROVED
			NO.	PERCENTAGE	NO.	PERCENTAGE	NO.	PERCENTAGE	
No urinary-tract damage.....	Susceptible	21	19	91	2	9	0	—	100
Urinary-tract damage.....	Susceptible	15	11	74	2	13	2	13	87
Totals.....		36	30		4		2		
Averages.....				83		11		6	95
No urinary-tract damage.....	Resistant	0	0	—	0	—	0	—	—
Urinary-tract damage.....	Resistant	4	0	—	0	—	4	100	—

*One patient was probably inadequately treated. Another improved markedly prior to the acquisition of resistance; despite the persistent bacilluria that continued after the acquisition of resistance the improvement was maintained during the follow-up period.

tein nitrogen was 165 mg. per 100 cc. and the blood carbon dioxide 17.2 milliequiv. per liter. Because of the marked impairment in renal function sulfonamides were contraindicated, and streptomycin was begun immediately on entry. The urine culture became negative within forty-eight hours, and the renal function began to improve. There is no doubt that streptomycin, in conjunction with fluid and salt replacement, was responsible for saving this child's life.

Nonspecific Urethritis

It appears that at least a portion of cases of urethritis that have previously been considered to be nonspecific, in the sense that they are nongonorrheal and nonpyogenic in origin, are due to infection by organisms belonging to the pleuropneumonia group.[15] On the basis that these organisms are small, gram-negative bacillary forms, it seemed worth while to try streptomycin therapy, although the sensitivity of the organisms in vitro had not been established because of technical difficulties.

Three cases of infection apparently due to pleuropneumonia-like organisms* were treated with streptomycin (Table 3). One of these cases was a simple urethritis (Case 1), 1 a urethritis associated with prostatitis (Case 2) and 1 a urethritis with hemorrhagic cystitis (Case 3). In all these cases no other micro-organisms could be isolated consistently from the urine. On the other hand, in Case 3 pleuropneumonia-like organisms were isolated from four urine samples, and in Case 2 in five instances from prostatic secretions or urethral discharges prior to the institution of streptomycin therapy. In Case 1 the fact that only one positive culture could be obtained despite repeated attempts is understandable in view of the difficulty associated with the isolation and cultivation of these organisms.

The urine was rendered alkaline in all cases. In Case 3 a total of 2.0 gm. of streptomycin was given intramuscularly daily (0.4 gm. every four hours, the 2-a.m. dose being omitted). Because of the improvement on the sixth day, the dose of streptomycin was reduced to 1.0 gm. daily, and continued for five additional days. Three days after the institution of therapy, there was less dysuria and urgency, the red and white cells in the urinary sediment were markedly reduced, and pleuropneumonia-like organisms could no longer be cultured from the urine. On discharge from the hospital the patient was entirely asymptomatic and remained so during a follow-up period of six months. This infection was of three years' duration, and during that time the patient had never been symptom-free for more than a few days.

The patient in Case 1 received 2.0 gm. of streptomycin intramuscularly daily for ten consecutive days. Improvement in urinary symptoms was noted forty-eight hours after the institution of therapy, simultaneously with a marked reduction in the number of red and white cells in the urinary sediment. Pleuropneumonia-like organisms could not be cultured from the urine after the institution of streptomycin therapy. Symptoms did not reappear during a follow-up period of four months.

In Case 2, a total of 4.0 gm. of streptomycin intramuscularly was given daily for eight consecutive days. On the day following the institution of therapy, the urethral discharge disappeared. Pleuropneumonia-like organisms, however, were consistently cultured from prostatic secretions and urine samples during therapy. The urethral discharge reappeared when streptomycin was discontinued.

TABLE 3. *Results of Streptomycin Therapy in Nonspecific Urethritis Apparently Due to Pleuropneumonia-like Organisms.*

CASE NO.	AGE	DURATION OF DISEASE	PREVIOUS THERAPY	STREPTOMYCIN DOSAGE DAILY	STREPTOMYCIN DOSAGE TOTAL	RESULT
	yr.			gm.	gm.	
1	49	2 mo.	None	2.0	19.2	Cure
2	34	16 yr.	Penicillin and sulfonamide	4.0	26.4	Failure
3	26	3 yr.	None	1.0-2.0	13.2	Cure

Haemophilus Influenzae INFECTIONS

Four cases of Type B *H. influenzae* infection were treated with streptomycin (Table 4). Two of these were meningitis, and 2 were epiglottitis. In addition to streptomycin the patients with meningitis received sulfadiazine. One patient also received 300 mg. of Type B *H. influenzae* antiserum. A *Quellung* reaction was not obtained, however, with this patient's serum, and it is doubtful whether the antiserum influenced the course of the disease.

Both patients with meningitis received 0.05 to 0.1 gm. of streptomycin intrathecally each day, as well as 0.6 to 0.8 gm. intramuscularly, divided into six daily doses given every four hours. The spinal fluid in both cases became negative for *H. influenzae* within forty-eight hours after streptomycin therapy had been instituted. Although a bacteriologic cure

*We are indebted to Dr. L. Dienes, of the Department of Pathology and Bacteriology, Massachusetts General Hospital, for the isolation and identification of these organisms.

was effected relatively early, clinical response was slower in appearing.

Two cases of *H. influenzae* epiglottitis requiring tracheotomy were treated with streptomycin. Each patient received 0.2 gm. every four hours intramuscularly. In both cases colonies of Type B *H. influenzae* were recovered from the pharynx as well as the blood. The patient in Case 3 received penicillin and sulfadiazine for two days before streptomycin therapy. Because the temperature remained high, the throat culture remained positive for *H. influenzae* and there seemed to be a spread of the pharyngeal infection, streptomycin therapy was started. On the following day the temperature dropped from 104 to 100°F., and *H. influenzae* disappeared from the throat culture forty-eight hours after the institution of therapy. In Case 4 streptomycin was started immediately on entry. Although much more severely ill on admission than the patient in Case 3, this patient had a much smoother convalescence and a shorter period of hospitalization.

TABLE 4. *Results of Streptomycin Therapy in* H. influenzae *Infections.*

Case No.	Diagnosis	Age	Duration of Disease	Previous Therapy	Streptomycin Dosage		Concurrent Therapy	Result	First Sterile Culture	Reactions	Remarks
					daily	total					
			hr.		gm.	gm.			days		
1	Meningitis	15 mo.	120	Penicillin and sulfonamide	0.8* 0.05–0.1†	5.9 0.35	Sulfadiazine	Cure	1	None	—
2	Meningitis	9 mo.	44	Penicillin and sulfonamide	0.6* 0.05†	7.2 0.35	Sulfadiazine; 300 mg. of antiserum.	Cure	2	Skin eruption	Blood culture positive for *H. influenzae*; *Quellung reaction* never obtained on blood serum.
3	Epiglottitis	11 yr.	48	Penicillin and sulfonamide	1.2	7.8	Tracheotomy and penicillin	Cure	2	Skin eruption	Infection extended into anterior and lateral aspects of neck
4	Epiglottitis and tracheobronchitis	3 yr.	15	None	1.2	10.6	Tracheotomy and penicillin	Cure	4	Skin eruption	Blood culture positive for *H. influenzae*

*Intramuscular route.
†Intrathecal route.

aerosol streptomycin was believed to be indicated. Doses of 2 cc. containing 50,000 units each of combined streptomycin and penicillin were inhaled every three or four hours. When combined therapy was employed the sputum was rendered sterile except for yeasts and fungi. Only 1 of the patients so treated was considered to have been benefited. Although no conclusion can be drawn from such a small number of cases, it appears that combined streptomycin and penicillin aerosol should be given further trial in cases of bronchiectasis.

A case of lung abscess, thought to be due to *H. influenzae*, since this organism was obtained in pure culture from the sputum, was treated with combined penicillin and streptomycin aerosol. The sputum was rendered sterile, and in twelve days there was marked improvement in the clinical con-

TABLE 5. *Results of Streptomycin Therapy in Miscellaneous Infections.*

Case No.	Diagnosis	Age	Duration of Disease	Etiologic Agent	Source of Culture	Previous Therapy	Streptomycin Dosage		Result
							daily	total	
		yr.					gm.	gm.	
1	Bronchiectasis	45	14 yr.	*Esch. coli*	Sputum	Penicillin* and sulfonamide	0.1†	0.7	No improvement
2	Bronchiectasis	50	9 yr.	*Esch. coli*	Sputum	Penicillin*	0.28†	1.44	Improvement
3	Bronchiectasis	79	? yr.	*Esch. coli*	Sputum	Penicillin*	0.2–0.24*	1.0	No improvement
4	Lung abscess	42	13 days	*H. influenzae*	Sputum	Penicillin* and sulfonamide	0.25	4.05	Improvement
5	Septicemia	1	21 days	*Ps. aeruginosa*	Blood, nasal washings, urine, stool and scalp abscess	Penicillin and sulfonamide	0.6–1.2	17.2	Cure
							0.6‡	5.0	

*Given as aerosol.
†Given as aerosol combined with penicillin in same nebulizer.
‡Given orally.

Miscellaneous Infections

Five cases classified as "miscellaneous" were treated with streptomycin (Table 5). Three of these were bronchiectasis, 1 a lung abscess, and 1 a case of *Ps. aeruginosa* septicemia.

The 3 patients with bronchiectasis were treated with streptomycin aerosol. These cases had been treated previously with penicillin aerosol with only slight improvement in the clinical condition. Because they continued to raise large volumes of sputum from which *Esch. coli* grew abundantly,

dition and the abscess cavity was considerably reduced in size.

One case of *Ps. aeruginosa* septicemia (Case 5) seems worthy of comment, since in view of the high mortality resulting from such infection, streptomycin is considered responsible for the recovery. The patient was an eleven-month-old child who had had diarrhea for two weeks and had been treated with penicillin and sulfasuxidine at another hospital. On admission to the Pediatric Service of the Massachusetts General Hospital the temperature was 106°F. *Ps. aeruginosa* was cultured from the blood, urine, stool and nasal washings. The patient was given 0.6 gm. of streptomycin daily, which gave a blood level of 16.0 microgm. per cubic centimeter. When the resistance of the infecting organism was found to be 16 microgm., the daily dose was increased to 1.2 gm. This dosage gave a blood level of 65 microgm. per cubic centimeter. The blood culture became negative on the third day of therapy, and the patient continued to improve. Several days later she developed a scalp abscess from which *Ps. aeruginosa* was recovered. In addition to intramuscular streptomycin she received 0.6 gm. of oral streptomycin daily, since she continued to carry an abundance of *Ps. aeruginosa* in the stools. After the institution of oral therapy, *Ps. aeruginosa* as well as *Esch. coli* gradually disappeared from the stool.

Discussion

Urinary-Tract Infections

Only a few publications have appeared describing the results of the streptomycin treatment of urinary-tract infections due to gram-negative bacilli. Herrell and Nichols[6] recorded good results in 10 of 13 cases, whereas Keefer et al.[11] reported recoveries in 42 per cent and improvement in 35 per cent of 409 cases. Less favorable results were obtained by Finland and his associates,[16] who observed failures in 8 of 12 treated cases, and Nichols and Herrell,[17] who reported good results in only 42 per cent of cases.

Of the 40 cases of urinary-tract infections reported in this paper, cures were obtained in 75 per cent and improvement in 10 per cent. Since these figures are somewhat higher than those reported in other publications, it seems worth while to compare the method of therapy employed with those used elsewhere. On the basis of the studies of Abraham and Duthie,[12] in which it was shown that there is a tenfold increase in streptomycin activity when the reaction of the urine is raised from pH 6.0 to 7.5, it seemed desirable to alkalinize the urine in all cases during therapy. In the 12 cases reported by Finland et al.[16] no attempt was made — with a single exception — to render the urine alkaline. Since no mention is made of this in the reports of Herrell and Nichols[6, 17] and Keefer and his co-workers,[11] such an effort was presumably not made. Because the route of administration of streptomycin, the daily dose and the duration of therapy were essentially the same in this study as those reported elsewhere, the higher percentage of good results is considered to be due to the fact that the urine was rendered alkaline in each case.*

Failure of streptomycin therapy in many cases has been attributed to the rapid development of resistance by the infecting organism. Finland et al.[16] showed that in 8 of 10 cases of urinary-tract infection the rapid acquisition of resistance was responsible for the failure of therapy. It is of great interest that in only 1 case of the 40 reported in this study did resistance develop. The only important difference between the method of therapy employed and those reported elsewhere was the insistence on an alkaline urine in each case during treatment. Accordingly, it seems highly likely that alkalinization is responsible for the failure of the organisms to develop resistance and, as a consequence, for the more favorable results obtained in this study. The mechanism for the failure to develop resistance in an alkaline medium is obscure. It cannot be entirely explained by the greater activity of streptomycin in an alkaline substrate, since in the cases in which the infecting organisms were not completely eliminated no increase in resistance could be demonstrated.

The results of the treatment of urinary-tract infections with streptomycin indicated that urinary levels above the minimal inhibiting dose of the infecting organism must be obtained if success is to be expected. If the minimal inhibiting dose of the organism is higher than the level that can be obtained in the urine, a resistant organism may be said to be present and failure will ensue. The presence of a susceptible organism does not necessarily indicate that a cure will result if marked structural damage is present, but minor and even moderate changes do not necessarily preclude a cure.

In this study it was decided to treat all cases regardless of the initial sensitivity of the organism to determine the relation between action in vitro and clinical response to the drug. Of the 40 unselected cases treated with a daily dose varying between 0.5 and 2.0 gm., 75 per cent were cured and 10 per cent were improved. On this basis it is believed that 2.0 gm. of streptomycin daily should produce satisfactory results in the majority of cases. Although the determination of organism sensitivity is desirable before institution of therapy, it is not essential. Since the urine became sterile in 83 per cent of cases forty-eight hours after the institution of therapy, if no clinical response is observed within that time, the sensitivity of the organism should be determined and the dose increased accordingly.

The variations in streptomycin sensitivity among strains of the same organism are well illustrated in

*Since the completion of this paper for publication an article on the favorable influence of alkali in streptomycin therapy of urinary-tract infections by Harris et al.[18] has appeared. In their series of 14 cases, 8 were cured. These investigators have noted that the maintenance of an alkaline urine during streptomycin therapy seemed to prevent the infecting organisms from acquiring resistance.

this series. For example, the sensitivity of different strains of *Esch. coli* varied from 1.5 microgm. (1.5 units) to more than 2.0 mg. (2000 units) per cubic centimeter. Other strains of *Esch. coli* that were inhibited by as little as 0.5 microgm. (0.5 unit) per cubic centimeter have been encountered in this laboratory. In general, the majority of strains of *Esch. coli* isolated were sensitive to concentrations of streptomycin that are easily obtainable in the urine, the resistant strains being the exception among this species. Three of the 4 resistant cases (Table 1) were infected with *Esch. coli*, whereas another was infected with both *Esch. coli* and *Pr. vulgaris*. These cases represent only about 10 per cent of all cases from which *Esch. coli* was isolated either alone or in combination with other organisms.

It seems to be the consensus that of the gram-negative bacilli, *Ps. aeruginosa* is the most uniformly resistant to streptomycin. Two of the four strains of this species, however, encountered in urinary-tract infections were found to be susceptible to fairly small amounts of streptomycin in vitro. These patients were cured of their infections. An additional case was cured, but unfortunately the organism could not be studied for sensitivity in vitro. In view of the clinical response, however, this strain was undoubtedly moderately sensitive, since a rather low daily dose of streptomycin was used. In only 1 of the 4 cases of urinary-tract infection due to *Ps. aeruginosa* was resistance in vitro encountered. This case did not respond to therapy. With the exception of Case 2 (Table 1), the strains of *Pr. vulgaris* studied were uniformly susceptible to streptomycin.

Because of the marked individual variations among strains of the same bacterial species, the clinical result cannot be predicted solely on the basis of species identification. For example, the infecting organism may be a resistant strain of *Esch. coli*, which as a species is considered to be susceptible to streptomycin. Likewise, a given infection may be due to a susceptible strain of *Ps. aeruginosa*, which as a species is generally considered to be moderately resistant to streptomycin. Bacteriologic response or sensitivity in vitro should be used as a guide to therapy; the former is perhaps preferable to the latter, since sensitivities in vitro and in vivo are not always parallel.

It might be noted that in mixed infections of Lancefield Group D streptococci (*Str. faecalis*) or *Staph. albus* and gram-negative bacilli, although streptomycin cleared the urine of the latter organisms, it failed to have any effect on the gram-positive organisms. It is also of interest that in 4 cases *Str. faecalis* or *Staph. albus* appeared in the urine after therapy was stopped. The majority of Lancefield Group D streptococci studied in vitro were resistant to the streptomycin levels obtained with the dosages used in this study.

Nonspecific Urethritis

Dienes and Smith[19] were able to isolate pleuropneumonia-like organisms from 4 cases of nonspecific chronic prostatitis. More recently, Beveridge et al.,[20] in Australia, were able to isolate these organisms in 20 per cent of 70 cases of nonspecific urethritis. These workers were unable to find this organism in the normal male urethra. It seems reasonable to assume that pleuropneumonia-like organisms may under certain conditions be responsible for nonspecific urethritis, prostatitis and cystitis.

Because pleuropneumonia-like organisms are small, gram-negative bacillary forms, it seemed worth while to determine the therapeutic effect of streptomycin on cases of nonspecific urethritis and prostatitis from which these organisms could be recovered. In 2 cases, within seventy-two hours of the institution of streptomycin therapy there was a marked decrease in the urethral discharge, as well as a decrease in the number of red and white cells in the urinary sediment. Pleuropneumonia-like organisms could not be recovered after the institution of streptomycin therapy. These patients remained symptom-free for the duration of follow-up periods of four and six months. The third patient appeared to improve while on therapy, but pleuropneumonia-like organisms never disappeared and a relapse occurred when therapy was discontinued. The disappearance of the organisms in 2 cases simultaneously with the onset of clinical improvement seems to support the bacteriologic evidence that pleuropneumonia-like organisms are responsible for certain cases of nonspecific urethritis, prostatitis and cystitis. Since the pleuropneumonia-like organisms probably do not constitute a homogenous group, the success or failure of streptomycin therapy depends in part on the susceptibility of the infecting organism. The failure of Case 2 to respond may have been due to the fact that the patient was infected with a resistant strain.

H. Influenzae *Infections*

Two patients with Type B *H. influenzae* meningitis treated with streptomycin recovered. In addition to streptomycin, both received sulfadiazine. One patient also received two doses of specific antiserum. Since a *Quellung* reaction was not obtained with serum from this case, it is doubtful whether the antiserum contributed to the recovery. In both cases the organisms disappeared from the spinal fluid after forty-eight hours of therapy.

The good results obtained in these 2 cases are similar to those reported by others in which antiserum was not used.[10, 11, 21] A recent report by Alexander et al.,[22] however, indicates that the severer cases of *H. influenzae* meningitis may require specific antiserum in addition to streptomycin and sulfadiazine.

Two cases of *H. influenzae* epiglottitis requiring immediate tracheotomy were treated with streptomycin. In addition, 1 patient received penicillin and sulfadiazine for two days before the institution of streptomycin therapy. Streptomycin was given in this case because throat cultures remained positive for *H. influenzae* and because there seemed to be a spread of pharyngeal infection. Forty-eight hours after streptomycin therapy had been started, the temperature had dropped considerably and *H. influenzae* disappeared from the throat. The other case, in which streptomycin therapy was started immediately on admission, had a much smoother and a shorter convalescence. These results indicate that streptomycin is a valuable adjunct to the treatment of *H. influenzae* epiglottitis.

Miscellaneous Infections

Three cases of bronchiectasis, whose sputums contained gram-negative bacilli predominately, were treated with streptomycin aerosol. All patients had previously been treated with penicillin aerosol with only slight clinical improvement prior to therapy with combined streptomycin and penicillin aerosol. In 2 cases *Esch. coli* disappeared from the sputum within four days of the institution of combined therapy. It is of interest that repeated sputum cultures failed to grow anything other than a few colonies of Monilia during and for some time after combined aerosol therapy. In both cases the sputum was reduced somewhat in volume, but in only 1 was there a simultaneous improvement in the clinical condition. In the third case, although there was a reduction in the number of colonies of *Esch. coli*, there was no diminution in the volume of sputum, nor was there any improvement in the patient's condition. These results indicate that although the sputum may be rendered sterile, clinical improvement may not ensue. This raises a question regarding the significance of the presence of *Esch. coli* in the sputum in bronchiectasis. In certain cases the organism is undoubtedly responsible for a low-grade infection, whereas in others it may simply be a commensural saprophyte. In the former case streptomycin therapy may prove to be of definite value, whereas in the latter, although *Esch. coli* can be eliminated from the sputum, clinical improvement may not follow.

One case of postoperative lung abscess believed to be due to *H. influenzae* was treated with combined streptomycin-penicillin aerosol. Previous to the addition of streptomycin, penicillin aerosol alone was used without improvement in the patient's course. After the institution of combined therapy, *H. influenzae* disappeared promptly, and there was a simultaneous reduction in the volume of sputum. The patient improved, and the abscess cavity was reduced in size. This case is still under observation.

Reactions

Eight of the 52 patients treated (15 per cent) experienced reactions that were considered to be due to streptomycin. These were relatively unimportant, and in most cases therapy was continued despite these manifestations. One patient complained of headache and vertigo, and 2 of pain at the injection site. Another developed a febrile reaction, and skin eruptions were observed in 4. The latter took the appearance of a papular, erythematous eruption that was somewhat pruritic. Three of the 4 patients who developed skin manifestations were children who, because of their small size, received a relatively larger dose than the adults.

Summary

Thirty-eight cases of pyelonephritis and 2 of cystitis due to gram-negative bacilli were treated with streptomycin. Cure was effected in 75 per cent, and improvement in 10 per cent, and 15 per cent failed to respond. Despite moderate renal damage and the presence of small nonobstructing renal calculi, cure resulted if the infection was due to a susceptible organism.

Patients infected with organisms with resistance in vitro greater than the levels that could be obtained in the urine with the dosage used in this study failed to respond. The acquisition of resistance by the infecting organism was not responsible for the failures reported. An appreciable increase in resistance was observed in only 1 case.

Two of 3 cases of nonspecific urethritis in which only pleuropneumonia-like organisms were isolated responded clinically and bacteriologically to streptomycin therapy.

Two cases of *Haemophilus influenzae* meningitis responded well to streptomycin therapy.

Recovery in 2 cases of *H. influenzae* epiglottitis seemed to be hastened by streptomycin therapy.

The favorable outcome in 1 case of *Pseudomonas aeruginosa* septicemia was undoubtedly due to the prompt use of streptomycin.

Of 3 cases of bronchiectasis in which *Escherichia coli* was the predominating organism in the sputum, only 1 showed clinical improvement as a result of treatment with combined penicillin and streptomycin aerosol.

One patient with lung abscess thought to be due to *H. influenzae* seemed to improve on combined penicillin and streptomycin aerosol.

Minor toxic reactions were observed in 15 per cent of cases.

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MEDICAL MOTION PICTURES IN PRIVATE PRACTICE*

DONALD W. LEONARD, M.D.†

EXETER, NEW HAMPSHIRE

PRIVATE practice, especially in rural communities, often makes an active physician believe that he is no longer practicing scientific medicine. He must fight the impression that the distance between him and the nearest medical center is directly responsible for the distance he seems to be from ever producing anything of value to medical science. When faced with the reality of a patient at home, he is sure to remember the skillful correlation of x-ray, laboratory and clinical facts that gave him such pride as an intern and to feel dismayed at the seeming hypocrisy of entering a private home to undertake treatment with no support beyond his own unaided judgment. Sooner or later, however, he will meet a new situation that would not have been possible in his beloved hospital, and some makeshift surgery or substitute drug will produce surprising results. With this will come the realization that his everyday work is actually a series of medical studies, and the success of his extemporizing will give him the comforting assurance that he has used originality equal to any that his former classmates could have shown in their research laboratories. This realization will bring a desire to share the observation with other physicians. The private practitioner will then need a medium of expression that has not been rigidly standardized but has concrete value as a presentation of the patient, even though it is technically incomplete because of its lack of bibliography, tabulated data and controlled experimentation. Amateur motion pictures will provide him with such a medium, and it is the purpose of this discussion to present evidence that the technics of motion-picture photography on medical subjects are well within the scope of a private practice.

Everyone has enjoyed motion pictures made by the popular producers in Hollywood. All of us are somewhat acquainted with the lusty offshoot doing profitable service in business advertising. Every physician has seen some of the films prepared in the large hospitals and clinics and having to do with operative surgery, medical education or public health. None of us have become sufficiently acquainted in a medical way with the humble amateur following his hobby in his own narrow circle but fully capable of producing pictures of professional clearness. Many a physician has been portraying the affairs of his own family but, with equipment right at his elbow, has never turned his hobby toward his medical work to discover how much it can enliven his practice with pictorial records of unusual cases. With the aid of motion pictures, a case history becomes an epic for demonstration at a medical meeting. To produce these films, the private practitioner needs information and gentle persuasion to convince him that motion pictures can be taken of his medical curiosities with equipment that does not require a studio and does not concern itself with darkrooms and film processing,

*An inquiry among active members of the New Hampshire Medical Society early in 1947 disclosed the following figures from the first two hundred replies: owners of motion-picture cameras, 65 (32.5 per cent), with 16 who had taken films of patients and 8 who had asked others to take pictures; physicians who did not own motion-picture cameras numbered 135 (62.5 per cent), those who had taken pictures with cameras belonging to others, 20, and those who had asked others to take pictures, 13. Potential motion-picture makers thus numbered 98, or 49 per cent of physicians who made replies.

Relatively few of the physicians in this "interested group" are specialists or are associated with clinics having photographic departments. It therefore seems that clinical motion-picture records in private practice should be emphasized as a practical development of this interest.

†Member, active staff, Exeter Hospital.

except in the remote headquarters to which he mails the film carton.

Subject Matter

The physician who wishes to record his experiences must not forget to make his sequence of pictures logical and systematic so that the interest of his audience will not be lost. Certain limitations in the choice of subject matter can wisely be observed. Subjective symptoms will give no pictorial impression, and the sickest patient will look at ease on the screen unless he is evidencing his inward discomfort by attitude, gesture or grimace. Records of most of the abdominal emergencies will be limited to pictures of the actual surgical procedures. Growths and external anomalies will lend themselves well to views before and after treatment. Fractures will have no pictorial significance unless there is obvious deformity or a well explained series of x-ray studies, although the technic of reduction and the apparatus for fixation will be excellent for the film record. Many of the limitations can be overcome by diagrams and charts, which are incorporated in the finished series of otherwise disjointed pictures.

Motion is the essence of this type of pictorial recording. It is almost too obvious to note that the presence of motion is the factor that gives medical motion pictures superiority over still pictures when the restoration of a function or an alteration of gait is a vital sign of clinical progress. If wanted, still pictures can be made by the thousand from the motion-picture film by the simple process of enlargement of single frames.

The private practitioner may carry out his medical filming along several lines, which may merge at many points. He may begin by taking pictures of all sorts of interesting cases and putting them all in a "medical scrapbook." Such views taken at random will often include different stages of progress in the same patient, and these can be removed from the collection to be spliced together with a few diagrams and explanatory titles to make a complete case record. A little planning in a case that promises interesting developments will usually result in a better medical thesis because it will be possible to arrange visual emphasis by comparisons with a normal and by the inclusion of extra pictorial data on tests that might not actually be required by the treatment. The medical motion-picture maker must be guided by foresight into the reactions of his future medical audience, and he must be bound by a self-imposed law that the material has to be of clinical importance and has to be presented in a colorful but still accurate manner.

Even though the private practitioner may not include in his daily work any actual surgery, he will occasionally be interested in following a case through the operating room. He will probably do this repeatedly in the same hospital and from experience learn the specific lighting conditions and the facilities for picture taking. Surgery offers the most spectacular but also the most exacting field for the amateur movie maker. Since the type of disease involved determines whether or not the procedure is suitable for pictures, the photographer must have the co-operation of the surgeon and must be ready to abandon his plans when there is deep dissection within the abdomen or in any similar cavity. Motion pictures under these conditions are beyond the reach of the usual amateur, and the procedures can be much better demonstrated by diagrams. Among the most favorable surgical subjects for motion-picture photography in the operating room are amputations, excisions of large tumors, plastic operations and others with similar obvious surface details. No better scenario was ever written than a cesarean section.

Technic

No one can talk about taking pictures of any kind without dwelling on the subject of exposure. For the motion-picture maker this detail has been reduced to a single step completed by setting of the size of the opening in front of the lens. The other camera factors remain standard because of their fixed relation to the speed of the action and of future projection. On most cameras there is a dial for setting the diaphragm according to the amount of light falling on the subject under conditions described in words that have been etched on a plate or printed card attached near the lens mount. The photographer must judge the suitable point according to these descriptions and set the aperture at the corresponding figure. The same figures are used in the directions that come with the film and with such accessories as photo-flood lighting units and title holders. With certain types of lighting and in definite places the motion-picture maker will discover that with his camera no satisfactory picture can be taken without artificial lighting or by moving of the subject into a better light. He will do well to learn early that an improperly exposed strip of film spliced into the finished film will spoil the effectiveness of otherwise excellent exposures.

Absolute rock-like steadiness of the camera while pictures are being taken is essential. Rapid swinging of the camera and even the small undulations caused by excited breathing will produce a giddiness that is distressing. Swinging of the camera during the taking of pictures is permissible only when there is a steady following of a moving object that itself retains a relatively fixed position in the frame of the picture or when slowly "tilting" or "panoramming" toward the center of interest across features of the scene that have such important bearing that they cannot be shown effectively in separate views. Thus, a close view of a patient with extensive edema can be obtained by moving slowly from the swollen feet to the region

of the face. A tripod is the standard means of securing steadiness for the camera. Other commercially made gadgets are available, but even without these assistants it should be possible for the photographer to hold the camera firmly enough in his hands and against his cheek regardless of the position of his body. In this manner, he can be sure of the greatest possible freedom to make quick changes in angle or position.

Lighting problems are quickly solved by photoflood bulbs. With these as a source of light, it is naturally easier to be sure of the proper exposure if there is no additional, unmeasured light from the sky. In medical filming the background is usually without special interest so that its loss in the dark shadows beyond the radius of effective artificial lighting can give the subject a detached importance that will compare well with views taken in other rooms and on other occasions. Instructions with the lighting units are sufficient for the determination of the aperture in relation to the number and distance of the lights from the subject. All types of panchromatic black-and-white film register correct color values with this illumination, but color photography under the same circumstances demands a special type of film that is balanced for artificial light and sold for this purpose.

In attempting to take motion pictures indoors by natural light the value of "top light" must be appreciated; its absence in any room that is without large windows makes this type of motion-picture photography extremely unsatisfactory. A few older hospitals still have top-floor operating rooms beneath skylights, but the good north light that these have been planned to provide will give the only favorable conditions that one can ever expect to find for indoor natural-light photography. There may be a temptation to use direct sunlight for indoor photography, but it must be remembered that sunlight through the limited area of a window sash will give lines of shadow from the window frame and contrasting light and shadow on the subject with a spotlight effect unless something is done to lighten the shady side.

Greater interest in medical motion pictures is created by a change in the camera angle for variety. This does not refer to camera angles that distort perspective or overemphasize certain characteristics because it is imperative that medical motion pictures avoid "trick photography" and retain scientific accuracy. There is, however, no reason for the monotonous use of eye-level views when the camera man can walk around the patient to take successive views just as a visiting physician would do if he were given the same opportunity. Variation of the angle and position of the camera in this manner will make the film record more human and natural for the future edification of a medical audience.

A sprinkling of close-up views will also give greater satisfaction when associated with more distant views of the whole subject. There is never a general view that does not contain a center of interest made so by its own arresting nature or by the subject of the demonstration. As soon as it is apparent that the audience will want to examine more closely, it is wise to be able to splice in a satisfactory close-up to show the details. The camera will then have done just what the average physician would have done if he had been in the presence of the patient. This feature may make the difference between success and failure when it comes to holding the attention of a medical audience.

The amateur camera man should be certain that the lighting, the camera angle and the distance from the subject are such that the picture recorded will show what is intended. It is obvious that the important part of the subject should be in the frame of the picture and not unintentionally cut off by one of its margins. This calls for reasonable care in framing the view accurately in the finder. This is more exacting with close-ups. If a view is intended to show a localized swelling, depression or pulsating blood vessel, there should be sidelighting to bring out the contour by a delineating shadow. These things may make necessary the moving of lights or the assumption of some odd position by the photographer but the results will be worth the trouble. Finally, it is suggested that the whole matter of picture taking be considered an art in itself and that the proportions of foreground, background and object of interest of each frame, as well as can be accomplished under conditions often too rigid to change, be artistically balanced, so that a degree of "finish" may be apparent in the completed film.

Editing and Titling

The step in the production of a medical film known as "editing" represents the carrying out of a plan that governs the selection of titles and the arrangement of film strips that may have been taken at widely separated occasions. The mainstay of the film editor is the process of film splicing. This step, whether done by hand or with one of the mechanical splicers, consists essentially of cutting the film ends, scraping away the emulsion and cementing the prepared ends together so that the sprocket holes on the margins of the film form a continuous series properly spaced. Each film editor in the amateur field can choose a plan that is entirely his own, but he may profitably copy many of the methods of cutting that he has observed on the professional screen. In medical pictures the emotional values are not of primary importance, so that the continuity of the film story need only follow the standard paths of medical reasoning to demonstrate or teach, holding the interest of the audience by the substance of the material rather than by the ingenuity of the producer. Editing should, however, strive to satisfy the medical

curiosity of future audiences. If the editor believes that this curiosity demands a close view, he should supply it; if it seems likely that a member of the audience unfamiliar with the material will want an explanation, he should place a title or a diagram at that point. Enough clinical data should be included in some manner along with the pictures to forestall any impression that the presentation is pointless. This all implies that the grouping of subjects should be tied together by a single theme either in the form of a discourse on one malady or as a frank presentation of the miscellaneous contents of a movie "scrapbook."

All films should be titled and edited before being shown to anyone except an occasional person who may have a direct interest in the care of the case. Complete editing means also that the material has been assembled according to plan, with the elimination of all unfit film as judged by any of the standards thus far discussed. Titling means the addition of written material or diagrams to supplement the pictures and round out the production into an understandable silent motion picture.

Projection at Medical Meetings

Projection of medical motion pictures made by the private practitioner for his medical associates represents the goal of the entire endeavor of their making. The finished film, deftly shown to a comfortable audience, gives the hobby its greatest justification, but this seemingly simple matter has its problems and an excellent film may be made less effective by bad conditions at the time of projection. The medical photographer will probably find that in his locality the audiences made up of his professional colleagues will be of about the same size each time they gather. The size of the group and the room in which the pictures are shown may therefore become familiar factors. In an informal group it always pays to ask certain members to move into positions between the projector and the screen before the film begins, and it is better, if possible, to have the screen only slightly above natural eye level, even if it is necessary to provide a center aisle. The carrying case of the projector may sometimes serve as a stand for the machine to bring it that much higher than the ordinary table top so that the rays of light will hit the screen at right angles to its surface. The distance should be so adjusted that the picture will completely fill the reflecting surface within the black borders of the screen without overlapping onto the wall behind.

Although the room for projection must be darkened in some way, it is recognized that absolute darkness is usually unnecessary. Unavoidable sources of light should be shielded from the eyes of the audience, and beams of light must be prevented from hitting the screen to give unequal illumination of the darker parts of the pictures. When color film is shown, it is wise to have less light in the room and to be sure that what little remains is without decided color of its own to unbalance the colors in the pictures.

As pointed out above, if the medical motion-picture maker wishes to establish and preserve a reputation, he must consistently refrain from showing his pictures until completely prepared for projection. He should never be forced to provide running comment to explain his continuity or excuse defective photography unless he plans to have someone read a prepared script through a microphone to simulate a sound film. His handling of the projector should be quiet and not accompanied by false starts, flashes of light, delays or rewindings. He can accomplish a smooth beginning by starting the motor of the projector before turning on the light as the first title appears, and make a graceful ending by turning off the light before the blank strip runs through to give a blaze of light on the screen. The exhibitor should try to have his machine as quiet as possible by proper oiling, by straightening bent reels and by the use of a rubber pad under the machine if it is necessary to absorb the vibration. His table for projection should be solid, his electrical connections tight, and his projector gate and lens clean, and he should have everything in readiness before his audience arrives. All this care for detail will reap dividends in satisfaction, and an already theater-minded audience will wonder how an amateur could obtain such pictures.

Summary

The groundwork for the production of creditable medical motion pictures by the private practitioner is discussed. The fact that motion pictures, as a field of medical expression, fall easily within the scope of a private practice is stressed. Any physician with simple equipment may obtain and use motion pictures to record his unique cases, because he has in his private practice the one vital thing necessary for such a visual record — the patient himself. No clinic or hospital has more than that.

CLINICAL NOTE

INFECTIOUS MONONUCLEOSIS COMPLICATED BY BILATERAL PAPILLORETINAL EDEMA

Report of a Case

John Ashworth, M.D.,* and
Salvatore A. Motto, M.D.†

CHICAGO

WITHIN the last decade the literature concerning infectious mononucleosis has often been reviewed by competent authors.[1–7] With each review the analyst has been careful to stress the variety of signs and symptoms manifested in this disease, which is not rare but frequently overlooked. Of all the reports that have been rendered, none has recorded the presence of a complicating transient, bilateral papilloretinal edema in the absence of a clinical picture of meningitis or encephalitis. An adequate description of the clinical picture of this disease, with special emphasis on the cerebral complications, was given by Thelander and Shaw[8] in 1941. In this report, however, no case of papilloretinal edema was recorded. Infectious mononucleosis with a complicating involvement of the central nervous system has been recorded since 1931,[9–11] but even in these reports, the predominant symptoms and signs were those of the clinical picture of meningitis or encephalitis or both.

The following case report proved to be of considerable interest to the staff of the Camp Grant Station Hospital because of the differential diagnosis that had to be considered in view of the history and physical findings presented. The laboratory data and subsequent course of the disease served to substantiate the diagnosis of infectious mononucleosis with a complicating bilateral papilloretinal edema.

D. C., a 19-year-old soldier, entered the Camp Grant Station Hospital because of nausea and vomiting of 7 days' duration. He had been a student in civilian life, and his career in the Army had been limited to the artillery. He had served in the Philippine Islands and had been in the United States only 2 months prior to admission. He had taken no quinacrine (Atabrin) for 2 months and had never had proved malaria. He had been hospitalized, however, for 10 days while in the Philippines, supposedly for dengue fever. He had been nauseated each day, with actual vomiting about twice daily, for 7 days before entry. The nausea usually occurred immediately after meals. He had felt hot during these episodes and had experienced an occasional slight chill, with pain low in the back. He had suffered no abdominal distress or pain, although the abdomen was "sore" from the repeated emeses. His appetite was considered poor, but there was no apparent weight loss. He emphasized the fact that the bowel habits were regular, as always, and that he had never noted any change in the color or character of the stools. Three days before admission, a moderately severe headache, associated with transient dizziness and only occasionally with vomiting, occurred. On entry the headache, as well as mild pains in the base of the neck, was still present. The patient made a note that he experienced distress in the eyes on movement of the eyeballs "up and down." Generalized weakness was apparent, but no difficulty in walking or controlling the extremities was manifested. At no time did he have chest pain but 36 hours before admission a nonproductive cough, which had become a source of constant annoyance, had developed.

The past history revealed measles and chicken pox in infancy, osteomyelitis of the left foot with sequestrectomy at the age of 8 years and an appendectomy, while the patient was still a civilian, in 1943. In November, 1945, a large boil developed on the right cheek just lateral to the right upper lip; the right side of the face became swollen, and hot applications were advised by a physician in an Army dispensary in the Philippines. The furuncle persisted for 1 week and then healed after a spontaneous discharge. The patient noted that he did not feel generally sick during this episode and was up and about. Venereal diseases were denied.

Physical examination revealed a 6-foot man who weighed 150 pounds and appeared to be well nourished, well hydrated and in no acute distress. The skin was warm and flushed, with no apparent rash or lesion. The conjunctivas were injected and excessively moist. Distress was elicited retrobulbarally with downward and lateral movements of the eyes; no spontaneous or elicited nystagmus was noted. The cardrums were intact, and each had a normal light reflex. Slight retraction, however, was noted in the left myringa. Fundoscopy revealed bilateral papilloretinal edema of 3 diopters, with no exudates or changes in the vasa. The neck possessed free mobility, but on extreme flexion the patient complained of some aching at the level of the seventh cervical and the first thoracic vertebras. The thyroid gland was not palpably enlarged. Examination of the oropharynx and nasopharynx showed moderate hyperemia. The palatine tonsils were small and not grossly infected. The lungs and heart were essentially normal. The abdomen was scaphoid and muscular, with a scar in the right lower quadrant, and was soft. No tenderness was noted, and the liver, kidneys and spleen were not enlarged to palpation. No masses were discovered, and the bowel sounds were normal. Examination of the genitourinary system, anus, rectum and bones and joints revealed no gross evidence of disease, and that of the lymphatic system disclosed the anterior cervical nodal chain to be moderately enlarged bilaterally; the lymph nodes, which were not tender, were soft and discrete. The muscular system revealed no swellings, atrophy, fibrillations, tenderness or definite weakness in any of the groups. The reflexes were physiologically brisk; no pathologic reflexes were elicited, and no reflexes were absent.

The temperature was 102.8°F., the respirations 24, and the pulse 110 and regular and of good quality. The blood pressure was 130/80.

A diagnosis of fever of undetermined origin was made, and further studies were anticipated in an attempt to disclose the etiology of the fever.

On the day of admission, a consulting ophthalmologist confirmed the presence of bilateral papilloretinal edema of 3 diopters. He concurred in the suggestion to perform a lumbar puncture. This was immediately done and revealed crystal-clear fluid under a pressure equivalent to 125 mm. of water, with normal dynamics. It contained 1 polymorphonuclear cell per cubic millimeter. The Pandy test was negative, the sugar, 52 mg., the total protein, 38 mg., and the chloride, as sodium chloride, 670 mg. per 100 cc. The specimen yielded no growth on culture and gave a gold-sol curve of 1221100000; the Wassermann reaction was negative.

An immediate peripheral blood smear revealed no malarial parasites, and x-ray examination of the chest was negative.

Urinalysis was negative. Examination of the blood disclosed a red-cell count of 4,800,000, with a hemoglobin of 15.0 gm. per 100 cc., and a white-cell count of 4800, with 96 per cent neutrophils, 32 per cent lymphocytes and 1 per cent monocytes; no abnormalities in morphology were seen at that time.

On the following day the temperature fluctuated between 101 and 102.4°F., but the patient stated that he felt better. Dysphagia and headache were the most annoying complaints.

*Formerly, attending physician, Cook County Hospital (Dr. Ashworth was recently killed in an automobile accident).

†Resident in medicine and, formerly, fellow in pathology, Cook County Hospital.

Physical examination was essentially unchanged. Complete neurologic examination revealed no abnormal signs other than those noted and recorded on admission. The total fluid intake and output, which were 2500 and 1148 cc., respectively, continued a normal course throughout the hospital stay.

On the 3rd day the temperature fluctuated between 100 and 104°F., and the lower pole of the spleen became palpable. Daily blood smears taken at the peak of the fever and several taken after the administration of 1 cc. of adrenalin revealed no malarial parasites. X-ray studies of the skull and visual-field examinations were essentially negative. The white-cell count remained under 10,000, and the differential count was within normal limits. The total serum protein was 6.4 gm. per 100 cc., with an albumin of 4.7 gm., the albumin-globulin ratio being 2.8. An agglutination test for Brucella organisms was negative, and the results of the heterophil-antibody study were not yet known; the Bence-Jones protein was normal. Repeated throat smears and culture revealed beta-hemolytic streptococcus and *Staphylococcus aureus*. A blood specimen taken for culture was negative. The blood Kahn test was also negative.

On the 5th day the hemoglobin was 15 gm. per 100 cc., and the white-cell count 6700, the differential count being within normal limits, but an occasional blood cell resembling the lymphocytic series and believed to be a prolymphocyte was seen. A sternal puncture revealed essentially normal bone marrow.

From the 6th to the 15th hospital day the white-cell counts began to rise and fluctuate between 13,000 and 22,150, the differential counts revealing 88 to 98 per cent lymphocytes, 10 or 15 per cent of which were prolymphocytes and 1 or 2 per cent so immature that they were difficult to differentiate from lymphoblasts. At least 5 per cent of the lymphocytes had fenestration and heavy, nuclear, chromatin network. The peroxidase stain was negative.

On the 11th hospital day the heterophil-antibody titer was 1:448. The blood specimen for this examination had been drawn on the 4th hospital day.

The repeated blood examinations, which revealed the lymphocytosis and fenestrated lymphocytes, the abnormal heterophil-antibody titer, the palpably enlarged spleen, the absence of anemia and the normal bone-marrow study substantiated the diagnosis of infectious mononucleosis.

To aid the patient during the period of extreme lymphocytosis, 40,000 units of penicillin was administered every 4 hours, and large doses of components of the vitamin B complex were given orally. Pyridoxine for intravenous use was not available.

The patient continued to run a low-grade intermittent fever, and on the 13th hospital day, while still on penicillin therapy, he developed an acute bilateral, lacunar tonsillitis. The temperature, however, never rose above 100°F. Within 3 days the throat signs and symptoms began to recede, and the temperature returned to normal and remained so until discharge from the hospital.

During the entire hospital stay, the patient was given complete neurologic examinations daily, but no disease other than that noted and recorded on admission was discovered. From the 18th hospital day until the 31st hospital day, the spleen gradually receded in size, until it was not palpable 7 days before discharge. A blood study on the 28th hospital day revealed that the lymphocytes were shifting back toward a normal percentage but were still 69 per cent, the neutrophils 25 per cent, the monocytes 3 per cent and the eosinophils 3 per cent. The papilloretinal edema had almost completely subsided.

On the 31st hospital day the patient was discharged feeling and looking well. The papilloretinal edema had completely disappeared, and the spleen was no longer palpable. The heterophil-antibody titer was still 1:448, but the white-cell count was 6000, with 50 per cent lymphocytes and 50 per cent neutrophils; no unusual white cells were apparent.

Summary

An unusual case of infectious mononucleosis with a complicating bilateral papilloretinal edema is presented. The history and physical findings suggested a variety of conditions, but the laboratory data and the course confirmed the proper diagnosis.

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MEDICAL PROGRESS

SERUM LIPIDS AND THEIR VALUE IN DIAGNOSIS (Concluded)*

SIEGFRIED J. THANNHAUSER, M.D.†

BOSTON

Normocholesteremia and Foam-Cell Formation

Increased xanthoma formation in essential xanthomatosis of the normocholesteremic type. This condition is synonymous with Schüller–Christian disease, lipid granulomatosis, eosinophilic granuloma and eosinophilic xanthomatous granuloma. Pinkus and Pick[87, 88] were the first to discover that the fat substances in the foam cells are cholesterol and cholesterol esters. These authors advanced the theory that cholesterol infiltration of certain cells takes place because of an increased cholesterol supply from the blood. In the syndrome under discussion, xanthoma-cell formation occurs without increased cholesterol supply from the blood — that is, with normal cholesterol values in the serum. Waldeyer[66] has already suggested that the xanthoma cell is an embryonal cell capable of forming different kinds of lipids, which are retained within the cell and released only by disintegration of these cells. Since reticulum cells and histiocytes may retain the functional possibilities of embryonal cells, it can be assumed that they are also capable of forming various kinds of lipids including cholesterol. It is conceivable that in these cells an inherent metabolic potentiality or a disturbance of the intracellular enzymatic systems concerned with the formation of cholesterol results in an accumulation of cholesterol within the cells, thereby transforming them into xanthoma cells (foam cells). It may be understood that under these abnormal conditions the excess of cholesterol found is retained within the cell and is not released into the blood stream. Such an explanation was applied by Thannhauser and Magendantz[43, 44] to the pathology of a systemic disorder showing xanthomatous and granulomatous features, which they designated as "primary essential xanthomatosis of the normocholesteremic type," singling out the normal cholesterol content of the serum as the leading clinical sign for differential diagnosis.

It was emphasized by these authors that certain organs may be involved singly or in various combinations in this systemic disease. The organs that may be affected are the skin (disseminated type of xanthomas), osseous system, dura, brain, lungs, pleura, liver, spleen and lymph nodes.[43, 44] Involvement of the dura, brain and osseous system is known as Schüller–Christian syndrome.[89] Rowland,[90–92] Chester[93] and Fraser,[94] in their pioneer work on the histology of the xanthomatous lesion in Schüller–Christian syndrome, had already demonstrated clearly that this lesion is granulomatous in nature (lipid granulomatosis). The presence of numerous eosinophils, as well as histiocytes and reticulum cells, in the granulomatous tissue had already been observed by these authors. These early investigators were, however, more impressed by the nests of foam cells in the granulomatous lesions than by the eosinophils and histiocytic elements and therefore designated the lesions as "xanthomatous" and the disease as "lipid granulomatosis" or "cholesterol granulomatosis." Ceelen,[95] in 1933, and Gerstel,[96] in 1934, suggested that the systemic granulomatous process is the primary feature of the disease, whenever foam cells appear in later states. In 1940 Lichtenstein and Jaffee[97] reported cases of solitary bone lesions of this disease. Fraser[94] had previously published cases with solitary bone lesions in an excellent and detailed study, describing and picturing the main histologic features of the lesions — namely, the reticulohistiocytic proliferation, the increase of eosinophilic cells in the granulomatous tissue and the gradual development of foam cells in the lesion. He designated such bone lesions as "lipoid granulomas." Lichtenstein and Jaffee apparently believed that this type of granuloma was a disease not hitherto described and named it "eosinophilic granuloma." It was not until the studies of Farber[98–100] and Engelbreth-Holm, Teilum and Christensen[101] that the designation "eosinophilic granuloma" was applied not only to single bone lesions but also to those of the Schüller–Christian syndrome, as well as to the generalized lesions in other organs of the group clinically classified by Thannhauser and Magendantz[43] as "essential xanthomatosis of the normocholesteremic type." Through the studies of Teilum and his co-workers it was histologically demonstrated that the natural history of such an eosinophilic granuloma comprised the following different phases: a proliferative phase in which reticulohistiocytic proliferation associated with accumulation of eosinophilic leukocytes is observed — in this phase there is no evidence of foam cells; a granulomatous phase, with increase of blood vessels and fibrils, reticular cells and histiocytes, eosinophils and giant cells (Touton cells) and incipient lipoid phagocytosis; a xanthomatous phase,

*From the Research Laboratory of the Boston Dispensary and the Joseph H. Pratt Diagnostic Hospital and the Department of Medicine, Tufts College Medical School.

This study was aided by grants from the Rockefeller Foundation, the Godfrey M. Hyams Trust Fund and the Charlton Fund.

†Professor of clinical medicine, Tufts College Medical School; associate chief, Boston Dispensary and Joseph H. Pratt Diagnostic Hospital.

with nests and isolated foam cells; and a fibrous stage, considered to be evidence of healing. These four phases often show no strict demarcation during the course of the disease, and their histologic features may overlap considerably during the course of the disease. The paper of Lichtenstein and Jaffee[97] has caused considerable misunderstanding about the classification of the disease under discussion, as is obvious from recent publications such as that of Weinstein and his associates.[102] It is evident that solitary eosinophilic granuloma is the monosymptomatic early stage of a systemic disease designated by Fraser[94] and Chester[93] as lipid granulomatosis, by Rowland[90–92] as Schüller–Christian disease and by Thannhauser and Magendantz,[43, 44] from the clinical point of view, as essential xanthomatosis of the normocholesteremic type. All these authors refer to the same disease. The designation of the disease in question as eosinophilic xanthomatous granuloma satisfies the clinical and the histologic observations, even if such a classification does not embrace the proliferative reticulohistiocytic phase.

urable increase of the normal constituents of this tissue, presupposing that a large specimen of this organ is used for the quantitative chemical analysis. For this reason, the quantitative analysis of a tissue specimen will not show a considerable increase of cholesterol originating from detritus of microscopic areas of focal necrosis, since the increase of cholesterol in one cell is balanced by the loss of cholesterol from another cell, which has previously undergone dissolution.

The quantitative chemical analysis of 0.5 to 2 gm. of tissue in the xanthomatous phase of eosinophilic xanthomatous granuloma shows an increase of ten to twenty times in the quantity of cholesterol as compared with the content of a piece of normal organ of similar weight. These high values of cholesterol found in the tissues cannot be considered as originating from cholesterol infiltration from the serum, since the cholesterol level of the serum in this disease is normal and since no analogous process is known whereby water-insoluble substances normally present in the serum infiltrate and accumulate in the cells. The enormous increase of cholesterol in the analyzed specimens of tissues during the xanthomatous phase of eosinophilic granuloma must originate in the organ itself as a result of increased cholesterol formation within certain cells capable of cholesterol synthesis. These cells, mostly of reticular and histiocytic origin, form and retain cholesterol, gradually developing the features of foam cells. The data presented in Table 3 illustrate this interpretation.

TABLE 3. *Lipid Partitions in Specimens of Tissue during the Xanthomatous Phase of Eosinophilic Xanthomatous Granuloma.*

TISSUE	TOTAL CHOLESTEROL %	FREE CHOLESTEROL %	CHOLESTEROL ESTERS %	TOTAL PHOSPHOLIPID %	SPHINGOMYELIN %	LECITHIN	TOTAL FATTY ACID	NEUTRAL FAT
Diseased lymph node[7]	17.90	2.20	15.70	6.4	Trace	—	—	—
Normal lymph node	0.60–2.30	0.50–1.10	0.20–1.20	5.5–11.0	0.5–4.5	—	—	—
Dura mater[100]	18.58	3.20	15.30	—	—	1.6	—	—
Skin[104]	4.55	3.66	0.89	—	—	—	3.64	—
Normal skin	0.15–0.30	—	—	—	—	—	—	—
Diseased liver[7]	7.25	4.55	2.70	7.4	—	—	9.05	0.71
Normal liver	1.10–2.60	1.50–2.10	0.45–0.55	9.0–11.0	—	—	8.60–13.0	1.4–4.0

The recent histologic studies of Farber[98–100] and especially of Teilum[101] contributed to a better understanding of the histology of the lesion. There is, however, an important point in which one may differ from the interpretation of Farber,[99] who does not regard xanthoma-cell (foam-cell) formation as one of the pathognomonic features of the lesion. He implies that the xanthoma cell, if present in the granulomatous tissue, develops by cholesterol infiltration into the cells. Cholesterol should originate from the detritus of focal necrosis and should be locally absorbed and stored by the macrophages. The following objections may be raised against this interpretation.

A considerable increase of a normal chemical constituent of a tissue can be the result of an infiltration of this substance into the cells due to an increased supply from the blood stream or of an increased formation of this substance within the cells of the tissue. A shift of a chemical cellular constituent from one cell, which has supposedly undergone dissolution, to another cell macrophagic in character will not cause a measXanthoma disseminata of the skin, the lesion characteristic of this group of xanthomatous granuloma, does not undergo visible necrosis, and microscopical examination reveals no extensive foci of necrosis, which could explain the extensive development of foam cells in the lesion.[104, 105]

Granulomatous lesions of the skin — like those in Hodgkin's disease, mycosis fungoides and infectious granuloma — show large areas of necrotizing processes even with macroscopically visible ulceration but no foam-cell formation. It is not understood why foam cells should arise only from the detritus of cells in eosinophilic

xanthomatous granuloma when they do not originate from the detritus of other granulomatous lesions in which large areas of necrosis are present. It is therefore unlikely that xanthomatous cell formation in the xanthomatous phase of eosinophilic xanthomatous granuloma is an accidental occurrence originating from the debris of local necrosis. It is, rather, suggested that during the abundant proliferation of reticulum cells and histiocytes in the earlier phases of the disease, cells that have preserved the inherent ability of the embryonal reticulum fat cell to synthesize and retain cholesterol within the cell arise and thus develop in a later phase into xanthoma cells (foam cells).[86]

Farber[98] states that he is not willing to accept the classification of Schüller–Christian syndrome in the group of lipid metabolic disorders. One can only agree with this consideration so far as this syndrome is not caused by a general disturbance of the *intermediary* cholesterol metabolism. For the consideration discussed above, it may be assumed that in the course of granuloma formation in the disease under discussion cells mainly of reticular and histiocytic origin intrinsically accumulate cholesterol as a result of an inherent metabolic potentiality or an intracellular metabolic disorder. These cells, which gradually develop the features of foam cells, are as pathognomonic in the later phases as the accumulation of eosinophilic cells is in the early stages of the disease. The evidence at present points to a formation of cholesterol within the cell rather than cholesterol infiltration for the explanation of the mechanism of xanthoma-cell formation in eosinophilic xanthomatous granuloma. For clinical considerations, however, the normal cholesterol content of the serum in this syndrome is an important feature for the differential diagnosis from other types of xanthomatoses.

Local accumulation of foam cells. A local accumulation of foam cells is occasionally encountered in inflammatory tissue or in a tumor growth, as in osteomyelitis, osteitis fibrosa, cystica disseminata, xanthomatous transformation of the mesentery and xanthoma cells in tumors. The serum cholesterol in such cases is normal. The mechanism of an occasional foam-cell development in a local, small, well defined area is not yet clarified.

Laboratory Procedures

The extraction of serum or wet tissue, according to Bloor,[106] is the basis of the determination of the total lipids and of the lipid fractions. This precedes all other analytic procedures. In the method for the determination of the total phospholipids the alcohol-ether extract is evaporated to dryness under reduced pressure or in an atmosphere of nitrogen; the dry residue is extracted with a small amount of petroleum ether from which the phospholipids can be precipitated by acetone and magnesium chloride and determined oxydimetrically after treatment with chromic acid. In this laboratory we prefer to determine the total phosphorus directly in the petroleum ether extract because the results obtained with this technic are not influenced by the presence of cerebrosides. Gortner[107] also concludes that the results obtained with phosphorus determination are more consistent than those obtained with the oxydimetric methods.

Folch and Van Slyke[108] described a different extraction procedure for the plasma lipids by which certain disadvantages of Bloor's procedure, such as the contamination of the final petroleum ether extract with nonlipid substances, can be avoided. The lipids are precipitated together with the proteins by colloidal iron in the presence of magnesium sulfate. Finally, they are extracted from the washed precipitate by an alcohol ether mixture at room temperature. In the event that one wishes to determine the lipids and their fractions in dry tissue, small pieces of the fresh material are immersed in ether cooled with solid carbon dioxide. The frozen pieces are dried in a vacuum desiccator over phosphorus pentoxide.

Various analytical procedures for the quantitative estimation of the phosphatide fractions have been devised. When they are combined with the determination of the total phospholipids, a fairly complete quantitative partition of a given phospholipid mixture is obtained. It should be pointed out, however, that the results obtained with different schemes of the partition show some discrepancies that cannot yet be completely explained. One of the difficulties encountered in this field arises from the necessity of hydrolyzing the lipids prior to the chemical analysis. Despite the fact that the general behavior of the lipids toward hydrolyzing agents is fairly well known, the conditions required for the quantitative hydrolysis of individual components of the various fractions have not as yet been studied sufficiently to exclude errors due to incomplete hydrolysis.

Phospholipids

The amount of amino nitrogen in phospholipid mixtures corresponds to the total amount of cephalins. The Van Slyke method is therefore widely used for the determination of cephalin in phospholipid mixtures. It must be emphasized, however, that unsaturated fatty acids evolve considerable amounts of inert gas with nitrous acid.[108] Folch, Schneider and Van Slyke[109] found negligible amounts of cephalin in the serum lipids when they took the precaution of hydrogenating the lipids before the determination of the amino nitrogen. Entenman and Chaikoff[110] obtained similar results by means of choline determinations in the plasma lipids. It appears that amino nitrogen determinations in the lipid mixtures should be carried out after the

removal of the fatty acids by a suitable method of hydrolysis.

A micromethod for the determination of the two known component nitrogen groups of cephalin — namely, ethanolamine and serine — has recently been reported by Artom.[111] It is based on the quantitative liberation of the nitrogen of either substance in the form of ammonia during the oxidation with periodate. When this method is combined with the quantitative separation of both substances by the selective adsorption of colamine on permutite, the amounts of either substance can be determined. In many tissues the sum of ethanolamine and serine as determined according to Artom's method agrees with the values for the total cephalin obtained by other methods. In some organs, such as the brain, kidneys and lungs, the figures obtained with the periodate method are too high, probably owing to the presence of sphingolipids in considerable amounts. It should be mentioned that Artom found considerable amounts of cephalins in blood plasma, contrary to the results obtained with some of the technics reported above. Blix[115] estimated cephalin in determining cholamine in hydrolysates of phospholipids by vacuum distillation under a pressure equivalent to 10 mm. of mercury at 75 to 80°C. and following acidimetric titration.

The sum of the choline-containing phospholipids (lecithin and sphingomyelins) can be estimated by the determination of the choline obtained after refluxing the lipid mixture for two hours with saturated barium hydroxide.[113] The best method for the determination of choline appears to be the spectrophotometry of its reineckate in acetone solution.[113] Amounts between 50 and 400 microgm. can be determined with an error of 5 per cent.

Taurog and his co-workers[114] achieved the separation of the choline-containing from the noncholine-containing phosphatides of liver by adsorption of the total phosphatides on magnesium oxide and selective elution of the choline-containing phospholipids by methanol.

The sum of the glycerol-containing phosphatides (lecithin and glycerol cephalins) is obtained by glycerol determinations in the dried phospholipid fractions, according to Blix.[115]

Attempts have been made to determine the glycerol in lipid extracts by periodate oxidation.[116, 117] The application of this principle to the analysis of fats appears to give reliable results. In the analysis of phospholipids, the use of periodate for the analysis of glycerol encountered two serious difficulties: the presence in the hydrolysate of interfering substances such as colamine and serine and the fact that the usual procedures for the hydrolysis of phospholipids do not lead to the liberation of glycerol as such but to the formation of a mixture of alpha and beta glycerophosphoric acid, the latter not reacting with periodate and thus escaping determination. It should be emphasized that alpha and beta glycerophosphate, rather than glycerol, should be used as test substances whenever procedures for the determination of glycerol in phospholipid mixtures are to be checked.

A convenient micromethod for the quantitative partition of phospholipid mixtures into monophosphatides and sphingomyelin has been developed by Schmidt et al.[118] When lecithin or cephalins are incubated with nitrogen and potassium hydroxide at 37°C. for fifteen hours, the total amount of their phosphorus groups become soluble in dilute acids, whereas the phosphorus of sphingomyelin remains insoluble under these conditions.

A direct microdetermination of sphingomyelin as acetone-insoluble reineckate has been described by Thannhauser, Benotti and Reinstein.[39] The sphingomyelin reineckate includes that of hydrolecithins, which have recently been found to be present in several tissues of brain and lung. Representative figures of the concentration of phospholipids in various tissues[86, 111, 119–121] and in isolated nuclei[122] have been reported by several authors.

Cerebrosides

A method for the determination of cerebrosides has been developed by Brückner.[123, 124] It is based on the colorimetric determination of galactose by means of orcinol and sulfuric acid in the hydrolysate of the lipid extracts. So far as specificity is concerned, it is superior to the earlier reductometric methods[125]; it should be mentioned, however, that Brückner's method cannot be applied to the determination of cerebrosides found in organs in Gaucher's disease.

Ottenstein, Schmidt and Thannhauser[37] have devised a method to determine galactosidocerebrosides and glycosidocerebrosides in organs that may contain both varieties of cerebrosides.

Cholesterol and Cholesterol Esters

Many methods of estimating total cholesterol and cholesterol esters have been published. The procedure of Schoenheimer and Sperry[126] requires more time than other methods but is the most reliable one for clinical use.

Total Lipid Fatty Acids

The total fatty acids in lipid mixtures are best determined by the method of Stoddard and Drury.[127]

Neutral Fat

There is no reliable method for the direct estimation of neutral fat (glycerol fatty acid esters) in lipid mixtures that contain other fatty acid esters like phosphatides and cholesterolesters. One must therefore determine the total fatty acids in a lipid mixture and subtract from the value obtained the quantity of fatty acids contributed by both the total phospholipids and the cholesterol esters. The remainder, when multiplied by 1.04, represents

TABLE 4. *Serum Analyses of Lipids in Various Diseases.*

CONDITION	TOTAL CHOLESTEROL	CHOLESTEROL ESTERS	FREE CHOLESTEROL	TOTAL PHOSPHOLIPIDS	LECITHIN	SPHINGOMYELIN	TOTAL FATTY ACIDS	NEUTRAL FAT	REMARKS*
	mg./100 cc.	*% total cholesterol*	*mg./100 cc.*	*mg./100 cc.*	*mg./100 cc.*	*mg./100 cc.*	*mg./100 cc.*	*mg./100 cc.*	
Normal values	150–260	70–75	40–70	150–250	100–200	10–30	200–450	0–150	
Essential xanthomatosis, hypercholesteremic type	350–800	Normal	100–250	250–430	220–400	Normal	500–900	Normal	Serum transparent; no increase in neutral fat; total fatty acids elevated because of high cholesterol esters and phospholipids; tuberous and plain skin xanthomas, tendon xanthomas and atheromas of blood vessels.
Xanthomatous biliary cirrhosis	800–2200	Normal	240–640	800–2000	770–1950	30–50	1000–2500	0–60	Serum transparent; no increase in neutral fat; total fatty acids elevated because of high cholesterol esters and phospholipids; jaundice of years' duration; in later stages total cholesterol decreases and ratio of cholesterol to cholesterol esters drops.
Essential xanthomatosis, normocholesteremic type (eosinophilic xanthomatous granuloma)	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Xanthoma disseminata of skin and eosinophilic xanthomatous granulomas of dura, brain, lung, osseous system, liver, spleen and lymph nodes occur singly, in various combinations or as a generalized form of the disease; no jaundice.
Idiopathic (familial) hyperlipemia, with hepatosplenomegaly and secondary xanthomatosis	300–600	60–75	90–180	260–500	240–420	Normal	2000–4000	1000–3500	Serum creamy; occasionally eruptive secondary xanthomas; influenced by diet.
Idiopathic hyperlipemia occasionally associated with slight diabetes	300–600	60–75	90–180	260–500	240–420	Normal	2000–4000	1000–3500	Serum creamy; severe degree of secondary eruptive xanthomas; influenced by diet.
Hyperlipemia associated with severe diabetes and secondary xanthomatosis	300–600	60–75	90–180	260–500	240–420	Normal	1500–3000	500–2000	Serum creamy; secondary eruptive xanthomas influenced by insulin.
Hyperlipemia in chronic pancreatitis, with secondary xanthomatosis	300–600	60–75	90–180	260–500	240–420	Normal	1500–3000	500–2000	Serum creamy; rarely secondary xanthomatosis; occasionally slight diabetes; other symptoms of pancreatic disease present; influenced by diet.
Hypercholesteremia associated with hypothyroidism	300–600	Normal	90–180	250–400	220–380	Normal	500–800	100–150	Serum transparent; rarely secondary xanthomatosis; influenced by thyroid and diet.
Hyperlipemia in lipid nephrosis	400–800	Normal	120–250	250–400	220–380	Normal	500–1000	150–400	Serum slightly milky; no secondary xanthomatosis; low serum protein.
Localized foam-cell formation (osteomyelitis, osteitis fibrosa cystica disseminata and xanthomatous mesentery)	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Serum transparent
Gaucher's disease	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Reticulum cells and histiocytes of bone marrow, spleen, liver and lymph nodes contain large amounts of glycoside cerebrosides; pigmentation in patches not present in all cases; infantile Gaucher's disease in generalized form and lesions are present in all organs.
Niemann–Pick disease	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Reticulum cells and histiocytes of all organs contain large amounts of sphingomyelin; cherry-red spot in macula of retina; observed in infants — rare in persons over two years.
Tay–Sachs disease (amaurotic idiocy)	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	No increase of sphingomyelin in organs; gangliosides increased in brain; cherry-red spot in macula of retina.
Hepatitis:									
Acute	260–400	40–60	100–260	Normal	Normal	Normal	Normal	Normal	Repeated estimations of the total cholesterol and of the ratio of cholesterol to cholesterol esters during the course of the hepatitis are helpful in the establishment of the prognosis of this disease. In contrast to hepatitis, the cholesterol esters remain in the first stages of occlusion on the borderline of normal; after a few weeks of occlusion the cholesterol esters decrease, being a sign of hepatocellular damage.
Chronic	300–400	30–40	210–280	Low normal	Low normal	Normal	Normal	Normal	
Acute-yellow-atrophy type	Less than 100	10–30	70–80	Lower than 100	Lower than 100	Low	Normal	Normal	
Complete obstruction of common bile duct by stone or tumor:									
Acute	350–400	60–70	Normal	Normal	Normal	Normal	Normal	Normal	
Chronic	400–500	40–50	200–300	Normal	Normal	Normal	Normal	Normal	
Biliary cirrhosis	260–400	40–60	100–280	Normal	Normal	Normal	Normal	Normal	
Compensated portal cirrhosis	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	
Alcoholic cirrhosis complicated by hepatitis and fatty liver	260–400	40–50	130–240	150–400	110–370	Normal	Normal	150–500	
Liver insufficiency of varied etiology	Less than 100	10–40	10–60	Low normal	Low normal	Normal	Normal	50–300	In conditions of liver insufficiency serum may be slightly milky; total fatty acids are normal, but neutral fat may be increased.

*Cerebrosides are not present in the serum in any of these diseased conditions.

neutral fat.[9] The formula for the evaluation of neutral fat is as follows:

> [Total fatty acids (mg. per 100 cc.) − [0.72 cholesterol esters (mg. per 100 cc.) + 0.69 total phospholipid (mg. per 100 cc.)]] × 1.04 = neutral fat (mg. per 100 cc.)

The factors 0.72 and 0.69 assume an average fatty acid molecular weight of 277. Erroneously, the value obtained for total fatty acids is often taken as equal to the value of neutral fat. For these reasons the values of neutral fat reported in the literature are mostly too high. In cases in which the cholesterol present as esters and phospholipids is high in the serum, the error is great.

It can easily be seen that by a suitable combination of several of the procedures discussed above it is possible to achieve a rather complete quantitative partition of the phospholipids. It must be emphasized, however, that the accuracy of figures obtained by calculating a difference should be carefully examined in each case. Only in tissues are the total lecithin and total cephalin fractions so large that errors of the individual determinations do not seriously interfere with the calculation of the difference.

In the laboratory of the Joseph H. Pratt Diagnostic Hospital the following procedures are adopted in the routine determination of lipids in the serum for diagnostic purposes.

For the determination of total cholesterol, free cholesterol and cholesterol present as esters the method of Schoenheimer and Sperry[126] is used. The only important change from the original method consists in the extraction of 1 cc. of serum in 25 cc. of acetone and alcohol (1:1).[128]

The total phospholipids, the sum of lecithin and cephalin and the sphingomyelin are estimated by the procedure of Schmidt et al.[118]

The total fatty acids are determined by the method of Stoddard and Drury.[127]

Neutral fat is evaluated from the figure obtained for total fatty acid minus the fatty acids present in cholesterol esters and phospholipids, according to the formula of Thannhauser and Reinstein.[9] For the evaluation of neutral fat it is therefore necessary to determine the total fatty acids, cholesterol esters and total phospholipids.

The normal values of lipids in serum, expressed as milligrams per 100 cc., with these methods are as follows:

Total cholesterol	150 to 260
Free cholesterol	40 to 70
Cholesterol esters	105 to 195*
Total phospholipids	150 to 250
Saponifiable phospholipids (lecithin and cephalin)	110 to 230
Sphingomyelin	10 to 30
Total fatty acids	200 to 450
Neutral fat	0 to 150
Cerebrosides	0

*Seventy to 75 per cent of total cholesterol.

Table 4 presents the results of serum analyses of lipids in various diseases.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

BENJAMIN CASTLEMAN, M.D., *Associate Editor*

EDITH E. PARRIS, *Assistant Editor*

CASE 33411

PRESENTATION OF CASE

A seventy-year-old widow was admitted to the hospital because of "feeling very bad."

One week prior to admission the patient found herself unable to get out of bed one morning and complained of weakness and pain in the legs. She also noted occasional twinges of pain across the chest, lasting only a few minutes. These symptoms persisted until the time of admission and added to them was increasing shortness of breath. There was no severe pain, paroxysmal dyspnea or cough. There was said to have been some fever at the onset of the present illness, but no chills had been noted. The patient had always been in good health until four years before admission when she developed diabetes, which was controlled by diet and insulin. One year before admission she was seen in the Out Patient Department for scabies. A medical check-up at that time uncovered a history of some dyspnea and ankle edema, and on physical examination the blood pressure was 150 systolic, 90 diastolic. The heart was not enlarged, but a gallop rhythm was heard; there was slight pitting edema of the ankles and occasional rales at the lung bases. No digitalis was given, and the diabetes was controlled with a diet and 12 units of protamine-zinc insulin daily.

There was no history of hypertension, angina, intermittent claudication or orthopnea. The weight had remained stationary.

Physical examination revealed a pale woman lying flat in bed. There were many old retinal hemorrhages. The neck veins were distended and pulsating. There were moist rales at both lung bases. The heart was enlarged, the area of dullness extending to the anterior axillary line, the rhythm was regular, with occasional extrasystoles, the sounds were somewhat distant, and to the left of the sternum in the fourth interspace was a rough, high-pitched sound, obscuring the first heart sound. This was believed to be a friction rub. The abdomen was protuberant but tympanitic in the flanks. The liver edge was felt one handbreadth below the costal margin and was firm and nontender. The spleen was enlarged to percussion. The ankle jerks and knee jerks were absent, and vibration sense was probably absent.

The temperature was 101.4°F., the pulse 90, and the respirations 28. The blood pressure was 130 systolic, 70 diastolic.

The urine gave a + test for albumin, a brown test for sugar and a + test for acetone; the sediment was normal. The hemoglobin was 10 gm. per 100 cc., and the white-cell count 9500, with 85 per cent neutrophils. The serum protein was 7.26 gm. per 100 cc., with an albumin-globulin ratio of 1.21, the van den Bergh reaction was 0.9 mg. per 100 cc. direct and 1.1 mg. indirect, and the cephalin-flocculation test was + in twenty-four and +++ in forty-eight hours; the cholesterol was 181 mg., the cholesterol esters 100 mg., the nonprotein nitrogen 50 mg., and the fasting blood sugar 227 mg. per 100 cc. The carbon dioxide was 25.4 milliequiv. per liter.

An x-ray film of the chest showed a heart shadow greatly enlarged in all diameters. There was fluid in the pleural sinuses, and the lung roots and markings were prominent (Fig. 1). A film of the abdomen showed a large gallstone in the right upper quadrant and a shadow in the left upper quadrant compatible with an enlarged spleen.

An electrocardiogram showed sinus tachycardia, a rate of 120 and a PR interval of 0.12 second, with an elevated ST segment in Lead 1 and a depressed ST segment in Lead 3. The T waves were upright in Leads 1 and 2, flat in Lead 3 and upright in Leads CF_3, CF_4 and CF_6; the complexes in the limb leads were low.

The course continued to be febrile, the temperature swinging from 101 to 103°F. On the second hospital day the heart rate became regular again at a rate of 90. The friction rub disappeared. In spite of digitalis, quinidine, insulin and oxygen the patient did poorly. On the fourth hospital day the breathing became Cheyne-Stokes in character, the neck veins became more distended, and the chest was filled with moist rales. There was no tenderness or swelling of the legs. The white-cell count was 15,500, with 95 per cent neutrophils. The temperature rose to 103.5°F.; the nonprotein nitrogen was 88 mg. and the fasting blood sugar 407 mg. per 100 cc., and the carbon dioxide was 26.2 milliequiv. per liter. On the fifth hospital day the temperature rose to 104°F., and the patient became unresponsive,

breathing rapidly. The heart sounds were distant and regular, the blood pressure was 110 systolic, 60 diastolic, and a paradoxical pulse was noted. Later during the same day the patient died.

Differential Diagnosis

Dr. Charles L. Short: May we see the x-ray films?

Dr. Stanley M. Wyman: This first film and the next film taken three days later show a grossly enlarged heart. Both films were taken with the patient in the supine position so that the exact size cannot be measured. There is no characteristic configuration. There is calcification in the region of the aorta, and in the lateral view the calcified area is seen descending in the chest. There is no gross dilatation of the pulmonary vessels. I cannot be sure of fluid in the pleural cavities, and it is impossible to exclude the possibility of fluid in the pericardial cavity. The patient has had an old fracture of the ribs, which I do not believe to be of any significance. The last film shows a gallstone, or an area of calcification described as being consistent with gallstone. It is difficult to see what is described as an enlarged spleen. I believe that the

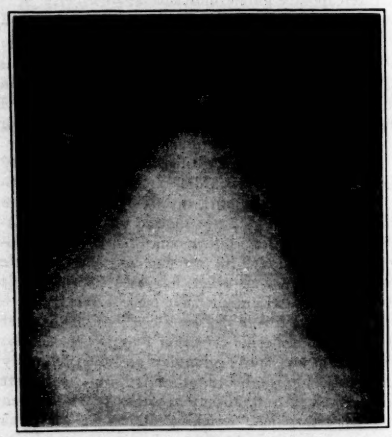

Figure 1.

spleen comes down to this point and is not definitely enlarged. I see no definite gas in the biliary radicles. There are no evident dilated loops of bowel.

Dr. Short: Is much pulmonary congestion apparent?

Dr. Wyman: I should say that there is very little x-ray evidence.

Dr. Short: No more than what one might expect with a heart of that size?

Dr. Wyman: The superior vena cava looks more prominent on the second film than on the first film, suggesting some degree of right ventricular failure.

Dr. Short: There is no question about one diagnosis in this patient — that is, the diabetes. This was at first mild and easily controlled with small doses of insulin, but at the time of admission it was resistant. At that time the patient had mild acidosis without appreciable lowering of the carbon dioxide. As a complication of diabetes she had evidence of retinopathy and probable peripheral neuritis, suggested by the weakness in the legs, the pain in the extremities and the absent reflexes. We must look beyond the diabetes, however, for the actual cause of death. It also seems clear that there had been some cardiac failure for at least a year and that at least some of the signs and symptoms of congestive heart failure had developed during the terminal illness. In addition, the fever and the leukocytosis suggest the presence of an infectious process at the time of and shortly before death. I think that we must first decide whether or not it is necessary to look outside the heart to explain the terminal illness. There was increasing nitrogen retention during the hospital stay. Were any further urine specimens available?

Dr. Tracy B. Mallory: Three urine examinations were done, of which two revealed no cells in the sediment and the other disclosed only one or two white cells per high-power field. Albumin was present in all in small amounts.

Dr. Short: Certainly, from the urine examinations, we cannot decide that the patient had pyelonephritis. I am thinking especially of the type that is frequently found in diabetes: necrotizing renal papillitis. This diagnosis should be considered in any diabetic patient dying with evidence of urinary infection and progressive nitrogen retention. But, in the absence of pus in the urine, I do not believe that it is possible to make that diagnosis, and in any case it would not explain the findings in the chest.

The enlarged liver and the probably enlarged spleen, together with a very slight degree of jaundice, draw attention to the liver. There was also a slight depression of the serum albumin and a positive cephalin-flocculation test. It seems, however, that in the presence of both diabetes and heart disease more positive evidence is needed before liver disease can be regarded as either a primary or a secondary cause of death.

We are left to determine the type of cardiac disorder present — one accompanied by high fever and by a pericardial friction rub. Rheumatic carditis and pericarditis are possible at any age, although they seem unlikely in this patient, especially in the absence of any characteristic murmur. Acute isolated myocarditis, or Fiedler's myocarditis, is a rare cause of cardiac enlargement and failure, usually accompanied by fever. Since I should need more

extensive electrocardiographic changes to make that diagnosis, I shall mention it only in passing, along with another type of heart disease with fever — abscess in the myocardium. Coronary disease, which is common in both male and female patients with diabetes, must of course be considered. That may have accounted for the cardiac failure a year before admission and for the terminal illness in the form of an acute infarction. There are certain features against the diagnosis of coronary infarction in this patient, however. The pain in the chest was not characteristic. There was no marked fall in blood pressure. The electrocardiogram is not specific for recent infarction in view of the normal anterior-chest leads, although the slight changes may be accounted for by a previous infarction in another region of the heart. The height of the fever would be unusual in coronary infarction unless there were involvement of an extensive area of the heart. I therefore doubt that an acute coronary infarction was the cause of death. Of course, the height of the fever may be explained by a lesion elsewhere in the body, especially pulmonary infarction, but we have no evidence in its favor. A more appealing diagnosis to me is pericarditis of a purulent nature, which is a rash diagnosis to make in the absence of sepsis elsewhere or in the absence of pneumonia. As Dr. Wyman has pointed out the x-ray studies are consistent with pericardial effusion. The friction rub is also consistent, as are probably the electrocardiographic changes. There are some atypical features about the patient that are helpful. When she came in she could lie down flat in bed, and as Dr. Wyman pointed out, there is very little x-ray evidence of congestive failure. This diagnosis would explain the high fever and, I believe, the other aspects of the case, except for the nitrogen retention, and I should therefore like to present it with some hesitation as the diagnosis.

DR. ALFRED KRANES: Would Dr. Short care to comment on the possibility of acute bacterial endocarditis? Having just missed a case at one of these conferences I bring it up for his consideration.

DR. SHORT: We have a patient who died with fever. We have no other positive evidence, have we?

DR. KRANES: No; except that attention is drawn toward the heart, and there was a questionably enlarged spleen. I do not see how one can establish the diagnosis, but perhaps one should consider it as a possibility.

DR. SHORT: Yes; I should have mentioned it as a possibility. I agree that there is not enough evidence to make the diagnosis, however.

DR. CONGER WILLIAMS: It should be emphasized that those who took care of this patient were limited to the objective findings. The history was entirely worthless because of language difficulty. We thought at first that the history did not suggest myocardial infarction. Later, on learning the electrocardiographic findings, we inclined more toward that diagnosis. We did consider pericarditis but thought that myocardial infarction was more probable.

CLINICAL DIAGNOSES

Myocardial infarction.
Congestive heart failure.
Diabetes mellitus.

DR. SHORT'S DIAGNOSES

Purulent pericarditis.
Coronary heart disease.

ANATOMICAL DIAGNOSES

Abscesses, myocardial, left ventricle.
Pericarditis, fibrinopurulent, acute.
(Diabetes mellitus.)
Hydrothorax, bilateral, moderate.
Pulmonary atelectasis, lower lobes, bilateral.
Cirrhosis of liver.
Rheumatic heart disease.
Endocarditis, chronic, rheumatic, mitral valve, slight.
Arteriosclerosis, generalized, severe, with ulcerations in aorta.
Intercapillary glomerulosclerosis.

PATHOLOGICAL DISCUSSION

DR. MALLORY: Autopsy showed a serofibrinous pericarditis and a greatly hypertrophied heart. On cutting into the heart we found a large abscess of the myocardium, and microscopically many smaller abscesses were observed throughout the myocardium. I think that the pericarditis was unquestionably secondary to the myocardial abscesses. The coronary arteries were markedly sclerotic, but none were occluded. The lungs showed only severe passive congestion — no pneumonia or infarction. Nowhere in the body did we find any other septic focus; there were no other abscesses to which this myocardial abscess might have been secondary.

There was a severe degree of cirrhosis of the liver of a rather nonspecific type that I could not classify. The organ was quite granular grossly, distinctly tougher than normal, and fat infiltration was present in some areas and absent in others. The spleen was hypertrophied, weighing 500 gm., and was fibrotic, indicating that there had been some significant degree of portal hypertension. The kidneys were slightly large, weighing 400 gm., and showed early changes of the type described by Kimmelstiel and Wilson[1] — intercapillary glomerulosclerosis. I doubt if the process had become sufficiently extensive to have had much to do with the symptomatology.

DR. ALLAN M. BUTLER: What did the culture show?

DR. MALLORY: A culture of the pericardium showed *Staphylococcus aureus*. In a survey of ab-

scesses of the myocardium in about 30 cases, reported by Weiss and Wilkins[2] some years ago, 80 per cent were due to the staphylococcus and the remainder to a scattering of other organisms.

DR. BUTLER: The post-mortem blood culture showed no growth?

DR. MALLORY: Cocci were present, and other organisms as well; there was undoubtedly a contamination.

DR. SHORT: Was there actual rupture into the pericardium, or was it involved merely by extension?

DR. MALLORY: Merely by extension.

A PHYSICIAN: Did the marked arteriosclerosis of the aorta have anything to do with it?

DR. MALLORY: There was marked sclerosis present. I cannot see any way in which it could have contributed to the symptoms.

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CASE 33412

PRESENTATION OF CASE

A fifty-two-year-old unmarried typist was referred to the Out Patient Department because of persistent cough and nervousness.

She had apparently been in good health until four and a half months before entry, when she noticed swelling and a dull pain in the legs, slight shortness of breath and a mild, persistent cough productive of white, mucoid sputum. She was then admitted to another hospital, where examination revealed hypertension, an enlarged heart, slight dependent edema and enlarged hilar lymph nodes on x-ray study. She was treated with digitalis, Schemm diet, iron and chest radiation, consisting of four doses of 200 r each. The symptoms cleared, but after six weeks there was still no change in the hilar lymph nodes. The patient was then told that she had Hodgkin's disease, whereupon she became disturbed and despondent. Two weeks before entry she noticed lumps on the right side of the neck. By that time she had lost considerable weight — from 160 pounds a year previously and 150 pounds four months previously to 132 pounds on admission.

The patient had had tuberculous cervical adenitis many years previously, and a hysterectomy had been performed for fibroids seven years before admission. Since then she had been subject to menopausal flashes.

Physical examination revealed a thin, nervous and anxious woman. The fundi showed only slight arteriovenous compression. In the neck there was scarring and induration under the right mandible. There were three hard supraclavicular nodules, 0.5 cm. in diameter, on the right and smaller, soft, palpable, anterior cervical lymph nodes. The lungs were normal. The heart was slightly enlarged, the border of cardiac dullness extending to the left. There was slight pitting edema, especially of the left ankle, associated with many telangiectases. Abdominal, pelvic and neurologic examinations were negative.

The temperature was 99°F., the pulse 80, and the respirations 20. The blood pressure was 215 systolic, 115 diastolic.

Examination of the blood disclosed a red-cell count of 4,380,000, with a hemoglobin of 13.8 gm., and a white-cell count of 8200, with 55 per cent neutrophils, 2 per cent large lymphocytes, 25 per cent small lymphocytes, 12 per cent monocytes, 4 per cent eosinophils and 2 per cent basophils. The total serum protein was 6.90 gm. per 100 cc., with 4.7 gm. of albumin and 2.2 gm. of globulin (albumin-globulin ratio of 2.1). The urine was normal. A guaiac test of the stool was negative, as was a blood Hinton test.

An x-ray film of the chest (Fig. 1) showed thickened lung roots and swelling of the right paratracheal lymph nodes. The lung markings were increased, and the left leaf of the diaphragm was obscured. The spleen was not enlarged.

A biopsy of a cervical lymph node was done.

DIFFERENTIAL DIAGNOSIS

DR. WILLIAM MCK. JEFFRIES: May we see the x-ray films?

DR. STANLEY M. WYMAN: These films show rather symmetrical enlargement of the lymph nodes at both hili, and there is apparently one large node in the right paratracheal region. The vascular shadows in both lung fields are diffusely prominent, and in the left lower-lung field there is some mottled infiltration, partially obscuring the diaphragm and apparently lying in the lower lobe. The heart shadow is slightly increased in size, enlargement being chiefly toward the left, possibly owing to left ventricular enlargement.

DR. JEFFRIES: The chief problem presented in this case is one of the differential diagnosis of the causes of enlargement of the mediastinal lymph nodes in a woman of fifty-two years. There are very few positive findings in the history, physical examination or laboratory studies that give a clue to the nature of the process.

The patient had noticed no symptoms until four and a half months before entry, at which time dyspnea, leg edema and a persistent productive cough developed. At another hospital she was found to have hypertension and an enlarged heart, as well as enlarged hilar lymph nodes, and after treatment with digitalis, iron and 800 r of x-ray therapy, the symptoms cleared without evident change in the size of the nodes, suggesting that the edema and dyspnea were due to hypertensive heart disease with failure. The cough apparently recurred, however, since we are told that it was a presenting com-

plaint at the time of admission to this hospital. When the lymph nodes failed to respond to x-ray treatment, the patient was told that she had Hodgkin's disease, but apparently no biopsy was taken — probably because no suspicious superficial lymph nodes had presented themselves at that time. Two weeks before entry here, however, lumps appeared in the right supraclavicular area. In the meantime she had lost 28 pounds during the previous year, 18 of which had been lost in the four months prior to entry. Some of this weight loss may have resulted from digitalization. We are not given any information regarding her appetite, but we are told that she

FIGURE 1.

had become disturbed and despondent after hearing that she had Hodgkin's disease, so that a good part of the weight loss may have been due to emotional disturbance rather than to the underlying disease.

We are therefore obliged to explain the cause of the enlargement of the mediastinal, right supraclavicular and anterior cervical lymph nodes, associated with productive cough of four and a half months' duration and weight loss, which may or may not have been related.

Could this patient have had Hodgkin's disease? That is certainly one of the most frequent causes of enlargement of mediastinal and cervical lymph nodes. It can occur at any age. Although it is somewhat more frequent in males, 30 to 40 per cent of reported cases have been in females. The description of the supraclavicular and cervical lymph nodes is compatible, since Hodgkin's nodes are usually rather discrete and may vary greatly in texture. The blood studies are not particularly helpful. This patient had comparatively normal red-cell and white-cell counts, with a slight increase of monocytes on the differential smear. Although patients with Hodgkin's disease most frequently show a normochromic or hypochromic anemia, with a moderate leukocytosis and an increase in the polymorphonuclear neutrophils, normal counts are not unusual. The eosinophil count of 4 per cent is at the upper limits of normal, but it is now realized that eosinophilia is not so common in Hodgkin's disease as it was formerly thought to be.

The history of failure of the mediastinal lymph nodes to respond to x-ray treatment is somewhat against Hodgkin's disease, although some radiologists report that a dosage of over 1000 r is necessary to cause decrease in size of some mediastinal lesions of this disease. The remarkably symmetrical enlargement of the hilar lymph nodes is also apparently unusual in Hodgkin's disease, so that it might be worth while to consider other possibilities in this case.

Other types of lymphoma should be considered, but here also the lack of radiosensitivity makes this diagnosis rather unlikely.

Could this have been tuberculosis? The history of tuberculous cervical adenitis many years previously is suggestive, but the paucity of clinical signs and the appearance of the mediastinal nodes on x-ray examination are unusual for this disease. Tuberculous mediastinal lymph nodes would not ordinarily be so large or so symmetrically distributed as those in this case.

Bronchiogenic carcinoma can likewise probably be dismissed on the basis of the x-ray picture of symmetrically enlarged hilar lymph nodes.

There is a condition, however, in which such symmetrical enlargement of the hilar nodes, accompanied by enlargement of the paratracheal nodes, and varying degrees of peripheral lymphadenopathy are described as characteristic — that is, Boeck's sarcoidosis.[1] It seems to occur most frequently in younger persons, the greatest incidence being in the third decade, but cases have been reported in patients up to seventy-four years old. The sex incidence is fairly equally distributed between males and females. A characteristic x-ray finding in addition to the striking enlargement of the mediastinal lymph nodes is pulmonary infiltration with linear or nodular densities.[2] There are few or no clinical symptoms, although the occurrence of cough has been reported in a few cases. It is remarkable that even in the presence of greatly enlarged hilar and paratracheal lymph nodes, there is usually no evidence of compression of the trachea or bronchial tree. So far as I know these nodes are not radiosensitive. The blood picture is not characteristic,

but the white-cell count is usually normal or low, and an increase in monocytes, with an otherwise normal differential, has been noted in some cases. An eosinophil count of up to 35 per cent has been reported in about a third of the cases. A striking feature found in many cases of sarcoidosis but not observed in this case is an elevation of the plasma globulin; the albumin and globulin were within normal range in the case under discussion. Characteristic areas of cyst-like rarefaction in the bones of the hands and feet have also been reported in approximately 10 per cent of cases in this country, but no mention is made of x-ray studies of the hands or feet in this case.

DR. WYMAN: X-ray films of the hands and feet were taken but showed no abnormality.

DR. JEFFRIES: That indicates that sarcoidosis was also suspected. Uveoparotid fever has also been reported in over a third of cases of this disease but was not present in this case.

The weight loss is unusual for sarcoidosis, but some loss of weight has been reported in a few cases and as I have already mentioned, this patient may have lost weight because of emotional disturbance or digitalization.

Finally, two other conditions that may cause chest x-ray findings of this nature should be mentioned. Coccidioidomycosis, or San Joaquin Valley fever is one, but the clinical course is similar to that of influenza or primary atypical pneumonia, chest pain being a prominent feature, and the white-cell count is usually elevated. Patients with this condition usually give a history of having visited or lived in the endemic areas of southwestern United States. The other is erythema nodosum, but in the absence of the classic skin lesions of this condition one could hardly make the diagnosis. It has been suggested by some that erythema nodosum is related to sarcoidosis, and erythema nodosum has also been reported in cases of coccidioidomycosis, so that the similarity of mediastinal x-ray findings may be more than coincidental.[3]

Therefore, we are left with two chief possibilities: Hodgkin's disease and sarcoidosis, and on the basis of the clinical picture, the x-ray findings and the resistance to x-ray treatment, sarcoidosis seems to have been slightly more probable.

CLINICAL DIAGNOSIS

Sarcoidosis?
Hodgkin's disease?

DR. JEFFRIES'S DIAGNOSIS

Sarcoidosis.

ANATOMICAL DIAGNOSIS

Sarcoidosis.

PATHOLOGICAL DISCUSSION

DR. BENJAMIN CASTLEMAN: Biopsy of the cervical lymph node showed the characteristic microscopical findings of sarcoidosis. The node was almost completely replaced by well formed groups of epithelioid cells in good tubercle formation. Langhans giant cells were present in moderate numbers. In a few places there were small areas of necrosis, but this finding does not mean tuberculosis. We have seen foci of necrosis in well established cases of sarcoidosis. It would be interesting to have had a tuberculin test; in the majority of cases with sarcoidosis, the tuberculin test is negative.

A PHYSICIAN: When the patient was seen in the Out Patient Department three months after the biopsy, no change was noted in her condition.

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The New England
Journal of Medicine

Formerly

The Boston Medical and Surgical Journal

Established 1828

Owned by the Massachusetts Medical Society and Published under the Jurisdiction of the Committee on Publications

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Material should be received not later than noon on Thursday, three weeks before date of publication.

The Journal does not hold itself responsible for statements made by any contributor.

Communications should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts.

GREATER BOSTON COMMUNITY FUND

Physicians are well aware of the need for the different kinds of service that more than three hundred Red Feather agencies of the Greater Boston Community Fund give to the people of this close-knit area of fifty cities and towns. Undoubtedly, they are familiar with the medical services offered, in which most of them probably take an active part. The medical profession is so close to the medical aspects, however, that the other valuable services to the community that the Red Feather symbolizes may be overlooked.

Of each dollar contributed last year, youth agencies and neighborhood houses received the largest share — 30 cents — for wholesome recreation for 290,562 people of all ages. Hospitals and dispensaries, which received 28 cents of the dollar, provided free or partly free care and 719,897 examinations and treatments for 28,435 patients. Next in line were family services, which received 19 cents of the dollar and which helped 20,773 families in time of trouble. Child-caring agencies — allotted 10 cents of the Red Feather dollar — gave 347,180 days of motherly care in foster homes to neglected children and 35,956 days to small children in day nurseries and nursery schools. Of the remainder of the dollar, 5 cents went to visiting-nurse care, 4 cents for the handicapped and aged, and 4 cents for fifty-four diversified special services.

Physicians affiliated with Red Feather hospitals may regard some of the services that they contribute as fulfilling the demands that the community makes on them. Money, however, is also needed to help meet operational expenses of all the Red Feather agencies, struggling against mounting costs in every field. It is well to remember that, whereas two out of five families in Greater Boston receive direct help from Red Feather services, everyone benefits in some way from the protection that these health and social agencies give to the community.

In the aftermath of war, the needs have increased — the old ones have been accentuated, and many new ones have developed. Family life has been disrupted and broken. Health and nerves have been taxed to the danger point. There is confusion and relaxation of normal standards. Young people are restless and undisciplined. Family and child welfare agencies probably bear the brunt of these increased needs as they face the situations caused by breaking of homes during the war, the soaring figures on illegitimacy, the unhappy young couples who married too hastily and the tremendous upsurge of juvenile delinquency.

Remembering that there are many needs beyond the call of medical duty, physicians should do their utmost to enable the Red Feather services to carry on in 1948.

SULFADIAZINE-RESISTANT STREPTOCOCCAL INFECTIONS AMONG CIVILIANS

At the height of the war, certain personnel of the armed services participated in a program of continuous prophylaxis with daily small doses of sulfa-

diazine in an attempt to minimize the number of man-days lost through streptococcal illness, particularly during the crucial initial training period. Among the possible complications that were expected to arise out of this program were the development and spread of sulfonamide-resistant strains of bacteria. The occurrence of such resistant organisms in military units was subsequently reported, and because of this the chemoprophylactic program was abandoned.

The mode of development of the resistant strains of bacteria has not been settled. It has been shown that strains of streptococci with slight degrees of sulfadiazine resistance appeared among Army personnel about the time when the program of mass chemoprophylaxis had already been in progress in the Navy for several months. It is possible that these slightly resistant strains were the precursors of the more highly resistant ones that later became established. It is also possible that resistant strains were transferred from certain Navy personnel who had been subjected to the prophylactic program and might have become carriers of the highly resistant streptococci. Interestingly enough, there was no evidence of the existence of sulfonamide-resistant strains of hemolytic streptococci prior to the institution of the mass chemoprophylactic program.

The evidence to date seems to indicate that all strains of hemolytic streptococci that were present in the civilian population prior to the time of mass chemoprophylaxis in the armed forces were susceptible to the action of sulfonamides. Furthermore, there is some evidence to show that the therapeutic doses of sulfonamides, as usually prescribed among civilians, do not cause the development of resistant organisms.

Since large numbers of personnel in the armed services were exposed to sulfonamide-resistant strains and since there were many opportunities for mingling of service personnel with civilians, it could be anticipated that sooner or later the resistant streptococci would be found among civilians. The occurrence of an outbreak of streptococcal infections due to a resistant strain has now been reported among civilians in a small community by Johnson and Hartman.*

Early in 1946 an epidemic of scarlet fever occurred in Cooperstown, New York. The first 8 patients that were studied were found to harbor Type 19 hemolytic streptococci. This was one of the types that had been found to account for a large proportion of the sulfonamide-resistant streptococci that spread among military personnel. It was decided, therefore, to determine whether the strains from this outbreak were sulfonamide-resistant. All eight strains were found to be resistant to sodium sulfadiazine in a concentration of 25 mg. per 100 cc.

This offered a unique opportunity to study the incidence of sulfonamide-resistant hemolytic streptococci in a small community. Cultures were obtained from patients living in Cooperstown and in the surrounding area of Otsego County who were suspected of having streptococcal infections. Strains from 100 patients were collected between the middle of February and the end of April, 1946. Two specific types were found to predominate: Type 3, which accounted for twenty-eight strains, and Type 19, which accounted for twenty-four strains. The remaining strains were of other specific types or could not be typed with the available diagnostic serums. All but one of the Type 19 strains were found to be sulfadiazine-resistant, whereas none of the remaining strains were resistant.

Of the cases of drug-resistant infection, 14 were clinical scarlet fever, and 9 were simple pharyngitis; 9 cases occurred in adults, and the rest were in children of school age or younger. The first case of scarlet fever occurred in a boy who was attending public school; following the onset of his illness, several of his classmates developed scarlet fever, and Type 19 sulfadiazine-resistant streptococci were isolated from all. The same organism was isolated from the parents, siblings and contacts of children originally infected in this public school. There were 3 patients, however, who had had no contact with any of these patients, nor had they had any known contact with recently discharged or active members of the armed services.

It is stated that these cases offered no particular therapeutic difficulties. It is not mentioned, however, whether any specific antibacterial agent, particularly sulfadiazine, was used. Obviously, if these cases were mild and if penicillin were used, no difficulties would be expected.

*Johnson, R. D., and Hartman, T. L. Sulfadiazine resistant streptococcal infections in civilian community. *J. Clin. Investigation* 26:325-328, 1947.

The development of resistance to antibacterial agents has become particularly important since the introduction of streptomycin. The emergence of streptomycin-resistant strains during treatment has been one of the most important factors limiting the successful use of that antibiotic. Drug-fastness, moreover, is the most important factor limiting the usefulness of the sulfonamides in the treatment of gonococcal infections. Fortunately, penicillin has been highly effective against infections with sulfonamide-resistant strains of gonococci. Furthermore, the widespread use of penicillin has thus far failed to give rise to penicillin-resistant strains to any significant extent. Whether attempts to use penicillin prophylactically on a wide scale or over a long period would result in the emergence of penicillin-resistant strains remains problematic.

In the meantime it is important to be on the lookout for the appearance and spread of pathogenic bacteria resistant to the chemotherapeutic and antibiotic agents, particularly in patients in whom the results of therapy with such agents are disappointing.

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

BROWN — Martin M. Brown, M.D., of North Adams, died on September 18. He was in his eighty-fifth year.

Dr. Brown received his degree from Rush Medical College in 1888. He had practiced medicine and surgery in North Adams for fifty-six years. He was a fellow of the American College of Surgeons and the American Medical Association.

CHARRON — Ovide Toussaint Charron, M.D., of New Bedford, died on May 26. He was in his sixty-fifth year.

Dr. Charron received his degree from College of Physicians and Surgeons, Boston, in 1912. He was a former member of the Massachusetts Medical Society.

COWLES — Frank Augustus Cowles, M.D., of Beverly, died on May 21. He was in his eighty-eighth year.

Dr. Cowles received his degree from University of the City of New York Medical Department in 1881. He was a former member of the Massachusetts Medical Society.

HIGGINS — George V. Higgins, M.D., of Randolph, died on September 8. He was in his sixty-seventh year.

Dr. Higgins received his degree from Tufts College Medical School in 1906. He was a former president of the Norfolk South District Medical Society and for thirty-five years was associate medical examiner for Norfolk County. He was a fellow of the American Medical Association.

His widow and three brothers survive.

JOHNSON — Mary W. L. Johnson, M.D., of Boston, died on September 15. She was in her eighty-first year.

Dr. Johnson received her degree from Women's Medical College of Pennsylvania in 1894. From 1905 to 1912 she was assistant superintendent of Inwood Sanitarium, Conshohocken, Pennsylvania, and in 1914 she founded Bellevue Hospital in Chestnut Hill.

A daughter and two nephews survive.

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New York Medical College, 1945.

MICHIEWICZ, MATTHEW S., 25 Main Street, Northampton.
New York Medical College, 1941.

WINSTEN, SOL S., Veterans Administration Hospital, Northampton.
University of Berne, Switzerland, 1939. Sponsor: Benjamin G. Morrison, Veterans Administration Hospital, Northampton.

F. Mary P. Snook, *Secretary*
Worthington

MIDDLESEX EAST DISTRICT

CODIN, KENNETH, 28 High Street, Stoneham.
Middlesex University School of Medicine, 1941. Sponsor: C. R. Hardcastle, 55 Elm Street, Woburn.

FOLDES, FRANCIS F., 8 Fenwick Road, Melrose.
University of Budapest, 1934. Sponsor: Jost J. Michelsen, 311 Beacon Street, Boston.

LEAVITT, HENRY E., 26 Maple Street, Stoneham.
Middlesex University School of Medicine, 1938. Sponsor: Howard A. Bouvé, 520 Commonwealth Avenue, Boston.

LEVINE, SIDNEY A., 5 Faulkner Place, Melrose.
George Washington University School of Medicine, 1941.

MCCARTHY, FRANCIS D., 229 Main Street, Melrose.
Tufts College Medical School, 1944.

MCLEAN, DONALD E., 81 Bacon Street, Winchester.
Harvard Medical School, 1943.

ORR, ROBERT B., 64 Westland Avenue, Winchester.
University of Virginia Department of Medicine, 1938.

REID, DAVID H., 274 Porter Street, Melrose.
Tufts College Medical School, 1943.

SOULE, ROBERT M., 8 Porter Street, Melrose.
Harvard Medical School, 1943.

SZDLOWSKI, SIGMUND J., 12 Richardson Avenue, Wakefield.
Middlesex University School of Medicine, 1941. Sponsor: Howard A. Bouvé, 520 Commonwealth Avenue, Boston.

WEST, GEORGE V., 22 Irving Street, Reading.
Tufts College Medical School, 1944.

YOUNG, JACK G., 7 Tremont Street, Stoneham.
Baylor University College of Medicine, 1940.

Roy W. Layton, *Secretary*
8 Porter Street, Melrose

MIDDLESEX NORTH DISTRICT

BARRY, JOHN J., 27 Milard Avenue, Chelmsford.
Middlesex University School of Medicine, 1941. Sponsor: Joseph D. Sweeney, 174 Central Street, Lowell.

BEER, ERNEST G., 66 Victoria Street, Lowell.
University of Heidelberg, 1923. Sponsor: Archibald R. Gardner, 16 Shattuck Street, Lowell.

BLUMENTHAL, IRVING J., Veterans Administration Hospital, Bedford.
University of Freiburg, 1937. Sponsor: Aaron H. Braverman, Veterans Administration Hospital, Bedford.

GRAINGER, HENRY B., Tewksbury State Hospital, Tewksbury.
Tufts College Medical School, 1943.

MEISLIN, JACOB, Veterans Administration Hospital, Bedford.
University of Lausanne, 1936. Sponsor: Morris Zellin, Veterans Administration Hospital, Bedford.

Brendan D. Leahey, *Secretary*
9 Central Street, Lowell

MIDDLESEX SOUTH DISTRICT

ABBOTT, RICHARD N., 6 Crocker Circle, West Newton.
Yale University School of Medicine, 1943.

APPEL, CHARLES F., 330 Mt. Auburn Street, Cambridge.
Jefferson Medical College of Philadelphia, 1941.

ARMSTRONG, BEVERLY W., 135 Washington Street, Brighton.
Syracuse University College of Medicine, 1941.

AVOLA, FRANCIS A., 17 Dwyer Circle, Medford.
Tufts College Medical School, 1944.

BARGER, A. CLIFFORD, 65 Strathmore Road, Brighton.
Harvard Medical School, 1943.

BASKIES, BARNET, 380 Salem Street, Medford.
College of Physicians and Surgeons, Medical Department Kansas City University, 1938. Sponsor: Henry M. Gahan, 19 Washington Street, Medford.

CROISSANT, EDWARD D., 371 Belmont Street, Belmont.
Middlesex University School of Medicine, 1940. Sponsor: Max Ritvo, 416 Marlboro Street, Boston.

DEXTER, CHESTER J., 1 Chiswick Terrace, Brighton.
Harvard Medical School, 1943.

DOMENICI, TRENTO J., 83 Bowdoin Street, Medford.
Marquette University School of Medicine, 1942.

DONOVAN, ROBERT E., 45 Hopkins Road, Arlington.
Middlesex University School of Medicine, 1940. Sponsor: Fred R. Jouett, 1 Craigie Street, Cambridge.

ETTENBERG, MAX, 120 White Street, Belmont.
Middlesex University School of Medicine, 1940. Sponsor: Jacob L. Rudd, 57 Lee Street, Cambridge.

GATES, PHILIP H., 4 Walnut Avenue, Cambridge.
University of Minnesota Medical School, 1937.

GORFINE, MORRIS, 897 Massachusetts Avenue, Cambridge.
Middlesex University School of Medicine, 1938. Sponsor: Jacob N. Newman, 140 Prospect Street, Cambridge.

GUENTHER, RICHARD A., 7 Revere Place, Medford.
Tufts College Medical School, 1943.

HESTER, JAMES W., 115 Mt. Auburn Street, Cambridge.
Tufts College Medical School, 1941.

INSERRA, FRANK, 336 High Street, Medford.
Tufts College Medical School, 1941.

JOSEPH, ALFRED T., 4 Shaler Lane, Cambridge.
Tufts College Medical School, 1943.

KAUFMAN, I. CHARLES, 215 Islington Road, Auburndale.
Long Island College of Medicine, 1943.

KROGER, LOUIS E., 90 Nonatum Street, Brighton.
University of Cincinnati College of Medicine, 1935.

KRUSH, THADDEUS P., 289 Park Street, Newton.
Western Reserve University School of Medicine, 1941.

KUBIN, LUDWIG, 19 Appleton Street, Waltham.
University of Vienna, 1920. Sponsor: Nathaniel P. Brackett, 826 Main Street, Waltham.

LAZANSKY, JOSEPH P., 14 Skahan Road, Belmont.
University of Prague, 1923. Sponsor: Ralph E. Wheeler, 416 Huntington Avenue, Boston.

LICHT, SIDNEY, 30 Hillside Avenue, Cambridge.
New York University College of Medicine, 1931.

LUCACER, MICHAEL, 1488 Cambridge Street, Cambridge.
Royal University of Palermo, 1926. Sponsor: Myer Marlin, 385 Broadway, Cambridge.

LYNCH, JOSEPH P., JR., 69 Tremont Street, Marlboro.
Boston University School of Medicine, 1943.

MACKENZIE, MICHAEL V., 20 Dutton Circle, Medford.
Tufts College Medical School, 1938.

NELSON, ROBERT E., 63 Chester Street, Arlington.
University of Oregon Medical School, 1937.

NEWCOMBE, RICHARD V., 8 Berkley Street, Arlington Heights.
University of Vermont College of Medicine, 1940.

NEWERLA, GERHARD J., 112 Vernon Street, Waltham.
Middlesex University School of Medicine, 1942. Sponsor: H. Quimby Gallupe, 751 Main Street, Waltham.

PICARIELLO, AMERICO, 104 Holland Street, Somerville.
Middlesex University School of Medicine, 1937. Sponsor: Anthony Russo, 2 Austin Street, Somerville.

PIOUS, LAWRENCE K., 255 Bedford Street, Lexington.
Middlesex University School of Medicine, 1940. Sponsor: Winthrop Harrington, 1900 Massachusetts Avenue, Lexington.

QUINN, EDMUND P., 153 Middlesex Avenue, Medford.
Tufts College Medical School, 1943.

RAPHAEL, SUMNER I., 15 Greycliff Road, Brighton.
Tufts College Medical School, 1943.

RILEY, LEO H., JR., 173 Jackson Road, Newton.
Boston University School of Medicine, 1943.

ROSENBAUM, JACK D., 35 Winter Street, Framingham Centre. Yale University School of Medicine, 1937.

SAPIENZA, PETER L., 683 Broadway, Everett. Boston University School of Medicine, 1943.

SENNOTT, FRANCIS W., 384 Broadway, Cambridge. Tufts College Medical School, 1943.

SNYDER, FRANKLIN F., 216 Arnold Road, Newton Centre. Johns Hopkins University School of Medicine, 1923.

SOULIOTIS, PAUL T., 330 Mt. Auburn Street, Cambridge. Hahnemann Medical College of Philadelphia, 1940.

TEDESCHI, C. George, Singletary Lane, Framingham. University of Bologna, 1929. Sponsor: Joseph C. Merriam, 198 Union Avenue, Framingham.

TIMBERLAKE, WILLIAM H., 10 Appian Way, Cambridge. Tufts College Medical School, 1943.

TROUBALOS, STEPHEN, 55 Brock Street, Brighton. Marquette University School of Medicine, 1943.

WEINREB, Joseph, 523 Ward Street, Newton Centre. Vanderbilt University School of Medicine, 1935.

Alexander A. Levi, *Secretary*
481 Beacon Street, Boston

NORFOLK DISTRICT

ABRAMS, ARTHUR L., 9 Gibbs Street, Brookline. Harvard Medical School, 1938.

BALLANTINE, HENRY T., JR., 180 Clyde Street, Brookline. Johns Hopkins University School of Medicine, 1937.

BREAN, HENRY P., Peter Bent Brigham Hospital, Boston. Harvard Medical School, 1943.

BREITWIESEN, EDNA R., Wellesley College, Wellesley. University of Pennsylvania School of Medicine, 1943.

BRUNNER-ORNE, MARTHA, 117 Winter Street, Westwood. University of Vienna, 1920. Sponsor: Sidney M. Bunker, Westwood Lodge, Westwood.

BURBANK, CHARLES B., 43 Sumner Road, Brookline. Harvard Medical School, 1938.

COHEN, MILTON, 132 Columbia Street, Brookline. Tufts College Medical School, 1939.

COLEMAN, NATHAN W., 235 Reedsdale Road, Milton. Middlesex University School of Medicine, 1941. Sponsor: Eli Friedman, 416 Marlborough Street, Boston.

CONDON, ROBERT V., 44 Westbourne Street, Roslindale. Tufts College Medical School, 1940.

DENNEN, WILLIAM I., 33 Wall Street, Wellesley. University of Rochester School of Medicine, 1942.

DRAKE, EMERSON H., 935 High Street, Dedham. Columbia University College of Physicians and Surgeons, 1941.

DRAKE, WILLIAM L., JR., 20 Netherlands Road, Brookline. Marquette University School of Medicine, 1943.

EMERSON, CHARLES P., JR., 29 Sheridan Road, Wellesley Hills. Harvard Medical School, 1937.

FOLEY, JOSEPH M., 19 Willis Street, Dorchester. Harvard Medical School, 1941.

GOLDSTEIN, ROBERT, 44 Stearns Road, Brookline. Harvard Medical School, 1937.

GRAY, WILLIAM, 166 Thorndike Street, Brookline. University of Nebraska College of Medicine, 1941.

HARWOOD, PAUL H., JR., 240 South Street, Chestnut Hill. Harvard Medical School, 1939.

HAYEK, AUGUSTA, 85 Naples Road, Brookline. University of Vienna, 1921. Sponsor: Blanche L. Atwood, 29 Powell Street, Brookline.

HOMANS, JOHN, JR., 33 Leicester Street, Brookline. Harvard Medical School, 1941.

KARRAS, JOSEPH D., 82 Stedman Street, Brookline. Middlesex University School of Medicine, 1937. Sponsor: Leon Rosenfeld, 371 Commonwealth Avenue, Boston.

KOENIG, ARTHUR T., JR., 41 Cliffmont Street, Roslindale. New York Medical College, 1943.

LARKIN, JOHN J., 215 Perham Street, West Roxbury. Harvard Medical School, 1939.

LIEF, PHILIP A., 29 Brookledge Street, Roxbury. New York University College of Medicine, 1941.

LYMAN, LEWIS, 152 Neponset Avenue, Dorchester. College of Physicians and Surgeons, Boston, 1937. Sponsor: Norman A. Welch, 520 Commonwealth Avenue, Boston.

MAISON, GEORGE L., 310 Harris Avenue, Needham. Northwestern University Medical School, 1935.

MASSIK, PAUL, 18 Alpha Road, Dorchester. Tufts College Medical School, 1942.

MELINE, DAVID I., 2089 Centre Street, West Roxbury. Middlesex University School of Medicine, 1937. Sponsor: Samuel N. Marnoy, 311 Commonwealth Avenue, Boston.

MILLEN, HYMAN, 999 Dorchester Avenue, Dorchester. Middlesex University School of Medicine, 1930. Sponsor: Humphrey L. McCarthy, 479 Beacon Street, Boston.

MONAHAN, JOHN L., 2 Laban Pratt Road, Dorchester. Tufts College Medical School, 1943.

MULLIGAN, WILLIAM J., 32 Cumberland Avenue, Brookline. University of Vermont College of Medicine, 1941.

O'HARE, JAMES M., 356 Newton Street, Chestnut Hill. Harvard Medical School, 1945.

POLATIN, SYDNEY, 4251 Washington Street, Roslindale. Middlesex University School of Medicine, 1942. Sponsor: Henry Baker, 453 Beacon Street, Boston.

RACIOPPI, FRANCESCA M., 152 Washington Street, Wellesley Hills.
Boston University School of Medicine, 1941.

RIEMER, ROBERT W., 62 Winter Street, Norwood. Tufts College Medical School, 1942.

SCHULTZ, JOHN D., 485 Heath Street, Chestnut Hill. Johns Hopkins University School of Medicine, 1937.

SHAUFFER, IRVING A., 4 Lawrence Road, Brookline. Tufts College Medical School, 1943.

SPELFOGEL, BENJAMIN, 20 Duke Street, Mattapan. Middlesex University School of Medicine, 1941. Sponsor: Jacob Chayet, 1807 Beacon Street, Brookline.

SPENCE, PHILIP S., 4648 Washington Street, Roslindale. Boston University School of Medicine, 1943.

SWEET, WILLIAM H., 35 Chestnut Place, Brookline. Harvard Medical School, 1936.

THOMPSON, WILLIAM J., 2076 Washington Street, Canton. Middlesex University School of Medicine, 1936. Sponsor: William F. Croskery, 1101 Beacon Street, Brookline.

TRAKAS, JOHN C., 102 Brook Road, Milton. Harvard Medical School, 1943.

VAUGHAN, ROBERT H., 29 Needham Street, Dedham. Harvard Medical School, 1943.

WALDINGER, CLARA, 17 Moraine Street, Jamaica Plain. University of Vienna, 1929. Sponsor: Marjorie Woodman, 21 Bay State Road, Boston.

WILSON, NORMAN J., 90 Ellicott Street, Needham. University of Maryland School of Medicine, 1935.

WIXTED, FRANCIS J., 630 Adams Street, East Milton. Middlesex University School of Medicine, 1941. Sponsor: John A. Seth, 47 Bay State Road, Boston.

YATSUHASHI, MASAO, Pondville Hospital, Walpole. Harvard Medical School, 1944.

Basil E. Barton, *Secretary*
10 Richwood Street, West Roxbury

NORFOLK SOUTH DISTRICT

CLANCY, DANIEL H., JR., 100 Washington Street, Weymouth. Tufts College Medical School, 1943.

CRISMOND, LOUIS A., 83 Independence Avenue, Quincy. George Washington University School of Medicine, 1945.

MCMAHON, FRANCIS J., 45 Snell Street, Holbrook. Boston University School of Medicine, 1942.

MESHORER, EDWARD, 15 Franklin Street, Quincy. College of Physicians and Surgeons, Medical Department, Kansas City University, 1938. Sponsor: Harold R. Record, 27 Temple Street, Quincy.

NALBAND, EDWARD H., 76 Watkins Street, Wollaston. Tufts College Medical School, 1943.

ORBACH, RUDI J., 279 Washington Street, Quincy. University of Milan, 1934. Sponsor: William S. Altman, 32 Spear Street, Quincy.

OSSEN, PAUL I., 208 Merrymount Road, Quincy.
Boston University School of Medicine, 1943.

RUBIN, FRANK F., 795 Southern Artery, Quincy.
Middlesex University School of Medicine, 1937. Sponsor: Frederick N. Manley, 1200 Hancock Street, Quincy.

TROTT, ARTHUR W., 253 Harvard Street, Wollaston.
Harvard Medical School, 1944.

WACKS, JOSEPH S., 76 Franklin Street, South Braintree.
Middlesex University School of Medicine, 1932. Sponsor: Nathan Zibel, 381 Bridge Street, Weymouth.

WHARTON, CARL M.. 56 Sycamore Street, Squantum.
Vanderbilt University School of Medicine, 1940.

WILSON, NORMAN L., 59 Coddington Street, Quincy.
University of Virginia Department of Medicine, 1940.

Ebenezer K. Jenkins, *Secretary*
Norfolk County Hospital, South Braintree

PLYMOUTH DISTRICT

ABDU, LOUIS, 64 Provost Street, Brockton.
Tufts College Medical School, 1942.

BLUMENTHAL, FREDERICK F., 9 Summer Street, Bridgewater.
University of Berlin, 1923. Sponsor: Alton L. Hurlburt, East Bridgewater.

BRITTON, LEE, 31 Clapp Street, Stoughton.
Boston University School of Medicine, 1945.

DONNELLY, JAMES F., 63 Franklin Street, Rockland.
Middlesex University School of Medicine, 1939. Sponsor: Joseph Dunn, 321 Union Street, Rockland.

GLEASON, CHARLES S., 121 High Street, Wareham.
Tufts College Medical School, 1946.

KAPLAN, MORRIS, Bridgewater State Farm, Bridgewater.
College of Physicians and Surgeons, Boston, 1937. Sponsor: Abraham L. Schwartz, Foxboro State Hospital, Foxboro.

LINGOS, JOHN W., 129 West Elm Street, Brockton.
Middlesex University School of Medicine, 1941. Sponsor: Ralph C. McLeod, 129 West Elm Street, Brockton.

MCENROE, DONALD F., 238 South Avenue, Whitman.
Middlesex University School of Medicine, 1939. Sponsor: George A. Moore, Moore Hospital, Brockton.

MAYO, W. VERNON, 119 Summer Street, Kingston.
Middlesex University School of Medicine, 1936. Sponsor: Harold H. Hamilton, 70 Court Street, Plymouth.

PASTER, HAROLD I., 106 Main Street, Brockton.
Middlesex University School of Medicine, 1934. Sponsor: Michael F. Barrett, 231 Main Street, Brockton.

PETRELL, NATALE R., 305 Court Street, North Plymouth.
Middlesex University School of Medicine, 1941. Sponsor: William E. Curtin, 272 Court Street, Plymouth.

THIERY, RAYMOND D., Bridgewater State Farm, Bridgewater.
Harvard Medical School, 1923.

WEIS, SAMUEL, 47 West Elm Street, Brockton.
Tufts College Medical School, 1930.

WHITING, GEORGE L., 317 Washington Street, Abington.
Tufts College Medical School, 1945.

Samuel Gale, *Secretary*
The Checkerton, Brockton

SUFFOLK DISTRICT

CALLOW, ALLAN D., 154 Beach Street, Revere.
Harvard Medical School, 1942.

CANNON, RAYMOND G., 942 East Broadway, South Boston.
Middlesex University School of Medicine, 1940. Sponsor: John J. Todd, 587 Beacon Street, Boston.

DAHL, LEWIS K., Massachusetts General Hospital, Boston.
University of Pennsylvania School of Medicine, 1939.

DEWING, NORMAN F., 868 Beacon Street, Boston.
Middlesex University School of Medicine, 1925. Sponsor: George P. Denny, 101 Bay State Road, Boston.

DIAMOND, ISRAEL, 174 Bay State Road, Boston.
School of Medicine of the Royal Colleges, Edinburgh, 1939. Sponsor: Frank E. Barton, 29 Bay State Road, Boston.

DOWNING, WILLIAM M., 195 Pilgrim Road, Boston.
Boston University School of Medicine, 1937.

FERRINO, PETER J., 21 Bennington Street, East Boston.
College of Physicians and Surgeons, Medical Department Kansas City University, 1938. Sponsor: G. Lynde Gately, 624 Bennington Street, East Boston.

GREGORIE, JOSEPH, 336 Sumner Street, East Boston.
Middlesex University School of Medicine, 1941. Sponsor: Edward J. Grainger, 200 Washington Avenue, Winthrop.

GREGORY, IRVING F., 390 Marlborough Street, Boston.
Tufts College Medical School, 1929.

HUNTRESS, WILLIAM W., 357 Charles Street, Boston.
Tufts College Medical School, 1938.

KENT, CHARLES, 270 Commonwealth Avenue, Boston.
University of Prague, 1927. Sponsor: Philip E. Meltzer, 20 Charlesgate West, Boston.

KURLAND, LEONARD T., 45 Beechcroft Street, Brighton.
University of Maryland School of Medicine, 1945.

LANE, HELEN E., 84 Byron Street, East Boston.
Boston University School of Medicine, 1943.

MEILMAN, EDWARD, 114 Riverway, Boston.
Harvard Medical School, 1940.

MORRIS, JOHN M., 264 Beacon Street, Boston.
Harvard Medical School, 1940.

OGLESBY, PAUL, 81 Pinckney Street, Boston.
Harvard Medical School, 1942.

PERKINS, HERBERT A., Boston City Hospital, Boston.
Tufts College Medical School, 1943.

PERRY, HELEN S., 97 St. Stephen Street, Boston.
Tufts College Medical School, 1943.

PICK, WALTER, Massachusetts General Hospital, Boston.
Harvard Medical School, 1942.

ROGERS, JOSEPH, 108 Jersey Street, Boston.
Harvard Medical School, 1941.

ROOPENIAN, ARAM, 716 East Seventh Street, South Boston.
Tufts College Medical School, 1942.

ROSENBERG, ISADORE N., 35 Allen Street, Boston.
Harvard Medical School, 1943.

SCANNELL, JOHN G., Massachusetts General Hospital, Boston.
Harvard Medical School, 1940.

SPELMAN, PHILIP J., 23 Colonial Road, Providence, Rhode Island.
Columbia University College of Physicians and Surgeons, 1940.

WARNER, FRANK A., 51 Mt. Vernon Street, Boston.
Harvard Medical School, 1935.

WHITNEY, BYRON V., 115 St. Stephen Street, Boston.
Tufts College Medical School, 1944.

WOOL, JACK, Boston City Hospital, Boston.
University of Vermont College of Medicine, 1941.

ZAMCHECK, NORMAN, 25 Shattuck Street, Boston.
Harvard Medical School, 1943.

Charles G. Shedd, *Secretary*
422 Beacon Street, Boston

WORCESTER DISTRICT

DOWD, GEORGE C., 216 Main Street, Worcester.
Middlesex University School of Medicine, 1941. Sponsor: Edward Budnitz, 16 Norwich Street, Worcester.

FLETCHER, MARY E., 10 Institute Road, Worcester.
Syracuse University College of Medicine, 1941.

FOWLER, RICHARD L., 125 Main Street, Spencer.
University of Maryland School of Medicine, 1943.

HADDAD, ALBERT, 18 Wall Street, Worcester.
Albany Medical College, 1943.

HEALY, THOMAS V., 21 Fiske Street, Worcester.
Harvard Medical School, 1943.

HECHLER, ROBERT, Veterans Administration Hospital, Rutland Heights.
Columbia University College of Physicians and Surgeons, 1931.

KAYE, ABRAHAM, Worcester State Hospital, Worcester.
Boston University School of Medicine, 1942.

MADOFF, IRVING M.. 5 Walker Place, Clinton.
New York University College of Medicine, 1943.

MANNING, JOHN J., St. Vincent's Hospital, Worcester.
University of Pennsylvania School of Medicine, 1941.

MARSH, CARL G., 390 Main Street, Worcester.
College of Physicians and Surgeons, Medical Department Kansas City University, 1942. Sponsor: Everett P. Jewett, 390 Main Street, Worcester.

MCKERNAN, BERNARD F., Main Street, Upton.
Middlesex University School of Medicine, 1939. Sponsor: Joseph I. Ashkins, 36 Pine Street, Milford.

REAGAN, DANIEL J., 507 Main Street, Worcester.
Harvard Medical School, 1939.

RICHMOND, PAUL, JR., 475 Main Street, Worcester.
Georgetown University School of Medicine, 1914.

ROY, JAMES E., 340 Main Street, Worcester.
Harvard Medical School, 1939.

STONE, TIMOTHY P., Southboro.
Tufts College Medical School, 1942.

STREETER, C. CLARKE, Harvard.
Tufts College Medical School, 1943.

YUDELL, MILTON H., 91 Elm Street, Worcester.
Rush Medical College, 1941.

Julius J. Tegelberg, *Secretary*
390 Main Street, Worcester

WORCESTER NORTH

ALEXANDER, DANIEL D., Gardner State Hospital, East Gardner.
Middlesex University School of Medicine, 1942. Sponsor: Charles E. Thompson, Gardner State Hospital, East Gardner.

BROWN, WESLEY C., Petersham.
College of Physicians and Surgeons, Boston, 1926. Sponsor: Donald B. Cheetham, 164 Exchange Street, Athol.

DUDIS, ROGER G., 521 Main Street, Athol.
Albany Medical College, 1943.

SILVER, JOSEPH M., 24 Prichard Street, Fitchburg.
Middlesex University School of Medicine, 1942. Sponsor: John J. Curley, 89 West Street, Leominster.

SPARLING, HAROLD J., JR., 1424 Main Street, Whalom.
Boston University School of Medicine, 1944.

SPARLING, SEDA A., 1424 Main Street, Whalom.
Boston University School of Medicine, 1944.

James G. Simmons, *Secretary*
30 Myrtle Avenue, Fitchburg

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

DIAGNOSIS OF UNDULANT FEVER BY LABORATORY TESTS

It is exceedingly difficult to make a diagnosis of undulant fever solely on the basis of clinical data. Among the diseases to be differentiated from it are infectious mononucleosis, tuberculosis, typhoid and similar enteric fevers, syphilis, malaria, subacute bacterial endocarditis, tularemia, Hodgkin's disease and rheumatic fever. In both the acute and the chronic phases of the disease, confirmation of the diagnosis rests on the relative evaluation of several specific laboratory tests: primary isolation of the Brucella organism by cultural methods from the blood, other body fluids or tissues of the patient; indirect recovery of Brucella by culture after animal inoculation; the agglutination reaction; and the intradermal and the opsonocytophagic tests. The first two procedures are self-explanatory and will not be discussed.

The *agglutination test* is most valuable diagnostically in acute cases. Agglutinins may appear as early as the fifth day but ordinarily do not until ten to fourteen days after the onset of the disease. Agglutination of Brucella antigen to titers of 1:135 is usually considered significant and presumptive evidence of an active infection with typical clinical symptoms. In some cases, particularly of the chronic type, agglutinins cannot be detected throughout the course of the disease. Furthermore, a significant agglutinin titer may not always indicate that the presenting symptoms result from active brucellosis. Agglutinins are present in the blood for many years after an infection. A positive agglutination merely indicates that the organism has successfully invaded the host ten days or more prior to the performance of the test. Furthermore, patients with tularemia may show agglutinins in low titer for Brucella, as may those treated with cholera vaccine (this may be confusing among former servicemen who received cholera prophylaxis) or infected with *Vibrio comma* (*V. cholerae asiaticae*). It has been reported that the serum of 3 to 9 per cent of patients with tuberculosis will give a false-positive reaction to this test; another study, however, has shown that a moderate number of patients with tuberculosis have had undulant fever at some time. Occasionally, cross-agglutination may occur in the presence of infection with *Eberthella typhosa*, *Proteus vulgaris* (X19 strain) and, more rarely, in other infections.

The *intradermal test* is an allergy test detecting sensitization to Brucella. An appropriate Brucella antigen (0.1 cc. of "Brucellergen," or 0.02 cc. of 1:10 dilution in physiologic saline solution of a bacterial suspension of 4,000,000,000) is injected into the skin of the flexor surface of the forearm. In positive cases, the reaction begins in twenty-four hours, rapidly spreading from 2 to 10 cm. in diameter, with erythema, considerable circumscribed edema and pain or itching, all of which may last up to nine days. The local reaction may be accompanied by an exacerbation of symptoms in infected patients and a mild systemic reaction in those hypersensitive to Brucella. A nonspecific reaction may appear within the first twenty-four hours, consisting of an area of erythema 1 to 2 cm. in diameter, which is of no significance and is rarely seen at the end of forty-eight hours. A positive cutaneous reaction signifies a past or present infection with Brucella.

It must be strongly stressed that whenever a skin test is to be performed, a blood sample for an agglutination test should be taken *before* the skin test. A false-positive agglutination test in low titer may result when the latter procedure is done after the skin test. This may be due to a previous exposure to the skin-test antigen. Secondly, a skin-test dose of antigen may act as a booster dose, elevating the Brucella agglutinin in titer in the serums of previously infected patients to a significant level (even though the Brucella is not contributing to the pre-

senting illness). Therefore, the intradermal test should be deferred until all information obtainable from the agglutination test has been secured.

The *opsonocytophagic test* as developed by Huddleson should be performed within seven days of the onset of the illness. In this procedure equal volumes of the patient's citrated blood and a saline suspension of living Brucella are mixed. After thirty minutes of incubation, a smear is made from the centrifuged mixture. The number of bacteria in 25 polymorphonuclear leukocytes is counted. If no cells are found in the leukocytes, the test is negative; if the number is less than 20, the opsonocytophagic power is considered to be slight, if between 20 and 40, it is moderate, and if over 40, it is marked. A positive skin-test reactor is considered infected if less than 50 per cent of cells show marked phagocytosis, questionably infected or immune if 50 to 80 per cent of cells show marked phagocytosis and immune if 80 per cent or more reveal marked phagocytosis. A negative skin test and little or no phagocytic activity indicate susceptibility to infection. It has been noted that patients infected with *Brucella melitensis* frequently show phagocytosis as high as immune subjects; therefore, a high opsonic activity does not always indicate immunity.

Other laboratory procedures have been employed in diagnosis, — namely, the precipitin and complement-fixation tests and various therapeutic tests,— but they have proved to be too inconclusive for wide general use.

No single test considered individually, with the exception of positive culture from the patient or through animal inoculation, is conclusive. All should be evaluated from a relative standpoint, and the results weighed carefully with the history and the clinical picture before a definite diagnosis is made.

Appropriate tests can be used to rule out the confusing diseases mentioned above. Agglutination tests for typhoid and paratyphoid B are routinely performed by the State Diagnostic Laboratory on all blood samples sent in for undulant-fever agglutination. On request, a heterophil-antibody titration for the diagnosis of infectious mononucleosis is done on the same blood.

CORRESPONDENCE

EFFECT OF LARGE DOSES OF IRRADIATION ON GASTRIC ACIDITY

To the Editor: The article by Dr. Irving B. Brick entitled "The Effect of Large Doses of Irradiation on Gastric Acidity," which appeared in the July 10 issue of the *Journal*, has been read with great interest. However, it seems to me to contain certain fallacies to which attention should be drawn.

In the first place the title and the article itself imply, and, indeed, state that the effect of large doses of irradiation on gastric acidity have been studied. In fact, the "radiation was delivered to the antrum of the stomach rather than to the upper part." It is a well recognized fact that the antrum does not secrete acid juice; the cells secreting acid and pepsin are located in the middle and upper portions of the stomach. Dr. Brick seems to take cognizance of this fact, but considers it only a "possible explanation." He specifically states that in previous studies using the 10 by 10 cm. portals described "it was shown that the effects both radiographically and pathologically are confined mainly to the *antral* and *pyloric* regions" (italics mine). How then can he draw any conclusion regarding the effect of irradiation on gastric secretion when he has not irradiated the acid-secreting portions of the stomach?

Furthermore, I must protest against the sweeping statement in the summary that "the use of radiation has no place in the treatment of peptic ulcer, since it has been shown that deleterious effects on the stomach can be obtained with this agent." Surely the author would not contend that all agents with which "deleterious effects . . . can be obtained" should be removed from our therapeutic armamentarium!

The demonstration by Dr. Brick of antral ulcers in 9 patients after intensive radiation of that region for tumor is important, but it is not pertinent to the problem of peptic ulcer. The lesions seem clearly due to radiation necrosis and are not analogous to spontaneous peptic ulcers. The susceptibility of the gastric and intestinal mucosas, and, indeed, of all living tissue, to irradiation, given in adequate dosage, is well recognized. The fact that radiation may produce tissue necrosis under certain circumstances does not prove radiation to be of no value under other circumstances. Specifically *if* radiation were able to destroy the acid-secreting cells of the gastric mucosa the procedure might be of very great value in the treatment of peptic ulcer, a disease, by the way, not entirely of "unknown etiology."

I regret the necessity of finding fault with an excellent study. As Professor A. J. Carlson has often said in effect: "Facts are never in error regardless of how wrong the interpretation may be." I am sorry that Dr. Brick did not restrict his discussion to the evidence presented.

WALTER L. PALMER, M.D.

Department of Medicine
University of Chicago

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Dr. Palmer's letter was referred to Dr. Brick, whose reply is as follows:

To the Editor: I wish to thank Dr. Palmer for the interest displayed and the astute criticism of some of the conclusions.

As pointed out in my article, these studies on gastric acidity were made on patients with normal stomachs. The effect of radiation, which was being given for malignant disease extrinsic to the stomach, on gastric acidity was of some interest in determining whether or not the course of radiation injury of the stomach was altered by the degree of gastric acidity. There did not appear to be any correlation of the course and degree of gastric acidity. While, with the technic of irradiation used in these cases, the major portion of the radiation is directed at the antral portion of the stomach, there is undoubted overlap of radiation effect of the upper portion of the stomach as demonstrated at operation (Bowers, R. F., and Brick, I. B., *Surgery* **22**:20, 1947). The most drastic injury appeared in the antrum and pylorus, but there appeared evidence of radiation effect throughout the stomach in the form of edematous thickening and avascularity. Submucosal edema and cellular changes of a nonspecific nature were noted histologically in sections from the fundus.

More relevant to the discussion is the careful study of Drs. W. L. Palmer and F. Templeton (*J. A. M. A.* **112**:1429, 1939) in which dosages of 1100 to 3600 r were directed to the upper portion of the stomach in patients with peptic ulcer. The charts accompanying the article reveal the extreme variability of reaction of gastric acidity to the radiation. One patient receiving 3600 r had a minimum depression of gastric acidity while another receiving only 1097 r had a rather prolonged depression (more than one hundred and sixty days). It is this extreme variability, which we also have encountered not only in the effect on gastric acidity but also in the radiation injury to the stomach, that deserves emphasis. Why some patients can receive 5000 to 6000 r and reveal no evidence of injury to the stomach and another patient receiving a dosage as low as 2424 r with the same technic (as in Case 9 in my article) will develop an ulcer, is a question of individual tissue tolerance to radiation worthy of further study. With the dosages used by Dr. Palmer, in 1 case receiving 2965 r hepatic necrosis was observed at operation and only a moderate depression of gastric acidity was ob-

tained. In another patient, who received 3227 r, study of the gastric mucosa was possible, since the patient died of an entirely unrelated coronary occlusion one day after completion of radiation therapy. The pathologist reported that "the mucosa revealed profound alterations everywhere, especially in the fundus." This, too, affords some evidence that there is apparent overlap of the radiation effect, since in these cases the radiation was directed only to the upper part of the stomach. Drs. Palmer and Templeton made no claim whatever for the efficacy of radiation in the treatment of peptic ulcer, nor did they advocate its use or delineate any place that such treatment might have in peptic ulcer. I have not been able to find in the literature the results of the continuation of this interesting study or any other using the same range of dosage of radiation.

It is from this study of Dr. Palmer and from my own that the conclusion that radiation has no place in the treatment of peptic ulcer was drawn. That conclusion should have been qualified by the addition of "with the dosages of radiation studied." For with the dosages used both in the cases of Drs. Palmer and Templeton and in my cases, the effect on gastric acidity was extremely variable, being unpredictable in the individual case, and the possibility of radiation injury was present. Furthermore, are we sure that over a longer period of observation there might not be progressive changes due to radiation? The well known progression and complications of x-ray skin burns may be an instance in analogy.

I can only agree with Dr. Palmer that "*if* radiation were able to destroy the acid-secreting cells of the gastric mucosa the procedure might be of great value in the treatment of peptic ulcer," but hasten to add that the dosage must be a safe one free of "potentially serious dangers in the treatment of a disease in which the group" with which Dr. Palmer is associated has had notable success by means of methods other than radiation. I believe that with the present knowledge of radiation effect on the stomach with and without peptic ulcer, the use of radiation in the treatment of peptic ulcer should be limited to investigative personnel doing carefully controlled clinical research, as illustrated notably by Dr. Palmer and associates. To date, no one has claimed to be able to produce destruction of the acid-secreting cells of the gastric mucosa with radiation, regardless of dosage.

In closing, I should like to call attention to a paper not available to me at the time of publication of my article in the *Journal*. Drs. Palmer, Levin, and Hamann (*Gastroenterology* 8:565, 1947), using dosages of radiation varying from 1350 to 1710 r over the body and fundus of the stomach, studied the effect on nocturnal gastric secretion in patients with duodenal ulcer. No toxic effects were noted. The variability of depression of gastric secretion in the period studied (fourteen to one hundred and fifty days) is again pointed out. Since the patients had received antacid therapy prior to radiation, this is not a strictly controlled study. No claim is made for the use of radiation in the treatment of peptic ulcer.

It is hoped that cases studied over a longer period will be available to determine the effect of safe radiation dosages on the chronic recurring disease that is peptic ulcer. Such a study may properly lead to a more adequate evaluation of the place that radiation holds in the therapy of peptic ulcer than I have been able to conclude from the available data.

IRVING B. BRICK, M.D.
Department of Medicine, Georgetown University
School of Medicine
Washington, D. C.

BOOK REVIEWS

Penicillin in Neurology. By A. Earl Walker, M.D., and Herbert C. Johnson, M.D. 8°, cloth, 202 pp., with 72 illustrations. Springfield, Illinois: Charles C Thomas, 1946. $5.00.

When penicillin was discovered as a therapeutic agent it was at once suggested as having probable value in diseases of the nervous system, particularly those due to infections. Although relatively nontoxic when given parenterally, the drug was not so innocuous when applied directly to the nervous system. If injected subcutaneously it did not reach the cerebrospinal fluid. Thus, for the treatment of meningitis and some infections, the drug had to be put directly into the intrathecal space. An effort was made, moreover, to apply it directly to the nervous system, particularly the brain when exposed by surgical means. The authors, who at the time this book was compiled, were in the United States Army, had wide experience in the use of penicillin. Dr. Walker was at the Cushing General Hospital, and Dr. Johnson served at the Lawson General Hospital.

Penicillin is somewhat toxic when given intrathecally or placed directly on the cerebral cortex. In this monograph the reactions are described both in man and in animals, and the indications for its clinical use are set forth in a clear manner. Time has changed the situation slightly, but the fundamental investigations reported in this work are still sound. Brief consideration is given to the treatment of syphilis of the nervous system and to the use of other antibiotic substances. The bibliography is adequate, and the illustrations are good. There is an adequate index. Since the book was written in the midst of active investigations and during a period of stress, owing to wartime activities, it cannot be considered a final report on the use of penicillin in the treatment of neurologic disorders. The monograph is strongest in the field of neurosurgery and relatively weak in that of the treatment of nonsurgical disorders.

Military Neuropsychiatry. Volume XXV of the *Proceedings of the Association for Research in Nervous and Mental Diseases*. 8°, cloth, 366 pp. Baltimore: Williams and Wilkins Company, 1946. $6.00.

The subject of military neuropsychiatry is reviewed by over forty-five investigators, most of whom were active participants in World War II. Practically all aspects of the subject are covered by the papers read and discussed at the annual session in December, 1944, of the Association for Research in Nervous and Mental Disease. Since the contributions were written in 1944, the later developments in 1945 are not covered. The volume sets a high standard and is useful as a record of papers in understanding the problems of the war neuroses, combat exhaustion, the psychotherapy of the soldier during conflict, the therapeutic use of drugs in narcosynthesis, craniocerebral injuries and the electroencephalogram, convalescent reconditioning and rehabilitation of discharged veterans. The authors include John E. Whitehorn, Roy R. Grinker, William C. Menninger, Howard P. Rome, Barnes Woodhall and Lewis J. Pollock. As usual in this series of volumes, the book is well edited and printed.

Fundamentals of Clinical Neurology. By H. Houston Merritt, M.D., Fred A. Mettler, M.D., Ph.D., and Tracy J. Putnam, M.D. 8°, cloth, 289 pp., with 96 illustrations. Philadelphia: Blakiston Company, 1947. $6.00.

The authors have attempted to give in two sections of the book an outline in some detail of the clinical examination of the nervous system and the methods used in arriving at a correct anatomic diagnosis in cases of structural diseases. In both endeavors they are successful, for this is a sound text, considering the limitations set up by the three men who collaborated in writing it. One is a clinical neurologist, another an anatomist, and the third a neurosurgeon. The book is designed for the use of practitioners and presumably for students of medicine. There are no references to the literature other than an occasional note on the source of an illustration. Although the book contains no material that could not easily be discovered in current texts on clinical neurology, the book will prove to be useful. Some of the illustrations, being clear-line drawings, are of particular value. The section on the examination of the nervous system is good and seems suitable to the aim of the book; that on anatomic diagnosis, which is far in advance of the general practitioner or beginning student, promises to be useful only for postgraduate students in neurology and, indeed, often goes beyond the material needed for anyone practicing that specialty. Because of this unevenness the book cannot be highly recommended. The authors have put together two unequal parts of clinical neurology, overfilling the pages with detailed anatomy, much to the detriment of the book as a whole.

A Handbook of Commonly Used Drugs, including Certain Measures for the Control of Diseases Peculiar to the Tropics of the Western Hemisphere. By Michel Pijoan, M.D., and Charles H. Yaeger, M.D., Dr.P.H. 8°, cloth, 198 pp. Springfield, Illinois: Charles C Thomas, 1947. $3.75.

This small book is largely compiled from personal experiences in the use of drugs, particularly in the tropics. It is a

condensation of larger works on the pharmacologic basis of therapeutics. Sound and clearly written, the volume should be of use. Although published this year, it is already outdated in certain aspects of the subject. To be of value, such a book should become a continuous product, the authors working on a subsequent edition even before the current one is published. A volume should probably be issued at least every three years. For example, most of the references used in the present book refer to articles published before 1940. In the section on endocrines there is no reference to the literature beyond that date, and yet the title page indicates that the purchaser is justified in expecting the literature to be covered at least through 1946. An even worse record is made in the reference under the therapy of syphilis, for the only work cited is one issued by the same publisher, an edition of 1933. This book, therefore, although valuable and well written, needs complete revision to bring it up to date.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Standard Methods of the Division of Laboratories and Research of the New York State Department of Health. By Augustus B. Wadsworth, M.D. With a foreword by Gilbert Dalldorf, M.D. Third edition. 8°, cloth, 990 pp., with 109 illustrations. Baltimore: Williams and Wilkins Company, 1947. $10.00.

This third edition of a standard reference work has been revised to include changes and additions made from 1939 to January 31, 1945, when Dr. Wadsworth retired from service. Changes will be noted in practically all sections of the text. A complete revision has been made in the routine methods for the serodiagnosis of syphilis. An outstanding change is the substitution of a new antigen composed of cardiolipin, lecithin and cholesterol for the cholesterolized alcoholic extract of beef heart that had been in use for several years. Certain methods in the fields of biochemistry and biophysics have been revised, and new procedures, as well as a new chapter on biologic assay, have been added. In the preface Dr. Wadsworth has given a brief history of the organization under which the methods outlined in the book have been formulated. The volume is recommended as a reference work for all medical laboratories and libraries.

Rehabilitation through Better Nutrition. University of Cincinnati Studies in Nutrition at the Hillman Hospital, Birmingham, Alabama. 8°, cloth, 94 pp., with fifty illustrations, some in color. Philadelphia: W. B. Saunders Company, 1947. $4.00.

This monograph summarizes the work carried on successfully since 1930 on persons suffering from deficiency diseases and treated by long-term nutrition therapy. It points out that malnourishment usually develops over a period of months or even years and that adequate results from nutritive therapy necessitate long treatment in many cases. From 1930 to 1936 the author studied 278 patients in Ohio with lesions typical of pellagra, beriberi or scurvy. In the Birmingham Clinic 914 patients suffering from various deficiency diseases were selected for study. These patients were afflicted with the vitamin deficiencies, including pellagra and scurvy, the various anemias with nutritive failure, nontropical sprue and protein deficiency.

Emphasis is placed on accurate diagnosis, and the first part of the monograph is devoted to a discussion of the various diseases from this point of view. A total of 10,851 persons were examined in the clinic from 1936 to 1945, and no evidence of nutritive failure was found in 5140 cases. From the remainder 914 patients with general nutritive failure severe enough to keep them from work were selected. At the final check-up examination in 1945, 21 were not available for various reasons, and the final study was therefore based on 893 cases. It is interesting that the Whites outnumbered the Negroes about 11:1, although the population of the community was equally divided.

All the patients included in the study improved promptly under the special treatment, gaining strength and weight, and were able to return to work, which they continued regularly.

The treatment consisted essentially of a high-calorie diet, supplemented by proteins, vitamins and minerals.

The principles of therapy used successfully in these cases were as follows: conditions causing excessive requirements were removed or relieved whenever possible; symptomatic treatment and therapy for coexisting diseases were given; it was made certain that the patient consumed daily a diet that supplied 3000 to 4000 calories, 120 to 150 gm. of protein and liberal amounts of minerals and vitamins; and therapeutic substances, such as dried brewer's yeast powder, liver extract and synthetic vitamins, were administered in sufficient amounts to correct the deficiency. It cannot be expected that these principles will be effective if the diagnosis is not precise or if the therapy is not persistently applied.

The text is well documented with tables, charts and case histories. The illustrations are excellent. A list of references concludes the text. The volume is well published in every way and is recommended for all medical libraries and to all physicians interested in deficiency diseases.

Diseases of the Nervous System. By F. M. R. Walshe, M.D., D.Sc., F.R.C.P. (Lond.), F.R.S., physician-in-charge, Neurological Department, University College Hospital, London, and physician, National Hospital for Nervous Diseases. Fifth edition. 8°, cloth, 351 pp., with 59 illustrations. Baltimore: Williams and Wilkins Company, 1947. (Printed in Great Britain.) $4.50.

The soundness and popularity of this small textbook is attested by the need of five editions in six years. The text has been brought up to date. The chapters on intracranial tumors and cerebral vascular disease have been rewritten. The volume is printed with a good type on good paper and, for the first time since the war, has wide margins pleasing to the eye.

NOTICES

AMERICAN ASSOCIATION ON MENTAL DEFICIENCY

The Northeastern Section of the American Association on Mental Deficiency will hold a meeting at the Wassaic State School, Wassaic, New York, on Saturday, October 18. After inspection of the school, followed by luncheon at 12:30 p.m., a regular meeting will be held.

PROGRAM

An Analysis of the Relationship of the Moron Group to State School Training. Drs. Ernest S. Steblen and Joseph E. Rosenfeld.

Social Service in the Realm of Mental Deficiency. Patrona F. Morgan.

Occupational Therapy with Mental Defectives. Percy H. Larrabee.

SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, OCTOBER 16

FRIDAY, OCTOBER 17

*9:00–10:00 a.m. Gastritis. Dr. Seymour Gray. Joseph H. Pratt Diagnostic Hospital.

*10:00 a.m.–12:00 m. Medical Staff Rounds. Peter Bent Brigham Hospital.

MONDAY, OCTOBER 20

*12:15–1:15 p.m. Clinicopathological Conference. Peter Bent Brigham Hospital.

TUESDAY, OCTOBER 21

*12:15–1:15 p.m. Clinicoroentgenological Conference. Peter Bent Brigham Hospital.

WEDNESDAY, OCTOBER 22

*9:00–10:00 a.m. Uterine Retrodisplacements. Dr. George A. Bourgeois. Joseph H. Pratt Diagnostic Hospital.

*12:00 m. Grand Rounds and Clinicopathological Conference (Children's Hospital). Amphitheater, Peter Bent Brigham Hospital.

*Open to the medical profession.

(Notices continued on page xv)